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# EXPERIMENTAL HYPOPHYSECTOMY.[1]

By S. J. Crowe, M. D., Harvey Cushing, M. D., and John Homans, M. D.

*(From the Hunterian Laboratory of Experimental Medicine, The Johns Hopkins University.)*

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## I. Introduction.

The function of one of the so-called ductless glands may be investigated by two principal methods. These may be designated as the positive and the negative methods of studying glandular physiology. The first embraces such procedures as the introduction of the gland or its extracts into the body by feeding or injection in order to produce reactions comparable to those which would be brought about by an exaggeration of the normal glandular activity. By the negative method observations are made upon the effects of lost or diminished function of the gland brought about by its complete or partial experimental removal—conditions therefore simulating grades of hypoactivity.

In the course of our work on the function of the hypophysis many experiments have been made by both of these methods, but the particular object of this paper is to record the results obtained by the indirect or negative method, which should enable us to determine:

(1) Whether the hypophysis, in whole or in part, is necessary for the maintenance of life.

(2) If essential, what symptoms occur antecedent to death.

(3) If not essential to life what effects, if any, are produced by its removal.

(4) Whether after partial removal of the gland definite symptoms supervene in consequence of diminished secretion, and whether a compensatory hypertrophy may occur.

(5) Finally, which of the anatomical subdivisions of the gland is chiefly responsible for the symptoms, if any, which follow the loss or mutilation of the structure as a whole.

In order to secure uncomplicated and trustworthy results by this indirect method of investigating glandular function it is

[1] Certain aspects of our investigations dealing with specific questions have already been published (Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine. *Quart. J. Exper. Physiol.*, 1909, II, No. 4, 389; The Experimental Production of Adipositas Universalis with General Atrophy (Hypopituitarism) to appear in Ziegler's Beiträge) and one of us (Cushing) has advanced some general views on the subject in an attempt to correlate the experimental findings with the clinical phenomena associated with various hypophyseal lesions (The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism. *J. Am. M. Ass.*, 1909, LIII, 249. Partial Hypophysectomy for Acromegaly, with Remarks on the Function of the Hypophysis. *Ann. of Surg.*, 1909, L, 1003. The Function of the Pituitary Body. *Am. J. M. Sc.*, 1910, CXXXIX, 473). It is anticipated that further papers dealing with the circulation of the hypophysis, the histologic appearance of the gland associated with varying grades of activity, the alterations of other ductless glands secondary to hypophysectomy, the effects of injection of extract in states of hypopituitarism, and a special discussion of the symptoms of polyuria, glycosuria, etc., will subsequently appear.

necessary, in the first place, that some procedure be devised by which the structure can be approached and manipulated with reasonable assurance of making a clean-cut lesion without complication from hæmorrhage, infection or from such injury of adjoining structures as might confuse the subsequent symptomatology. It is here that the introduction of modern surgical methods in experimental physiology plays its chief rôle, particularly in the case of structures as difficult of access as is the pituitary body. In the second place, past experience has shown that it is absolutely essential to make a thorough post-mortem microscopic study of the infundibular region, for naked-eye appearances do not justify one in passing judgment upon the totality of removal.

In order to fully interpret the confusing results of past experimentation, it is necessary to bear constantly in mind these two important factors, for one or the other of them has usually been wanting.

## II. Historical Review.

Reports have been made upon the effect of experimental hypophysectomy carried out on a variety of creatures—frogs, tortoises, chickens, guinea-pigs, rabbits, cats and dogs. In the attempt to find a satisfactory surgical route to the gland in one or another of these species, numerous procedures have been advocated. These may be subdivided into extracranial and intracranial methods of approach to the sella turcica. By the *extracranial* method the gland has been approached from below in the mid-line through the nasal, buccal, hyoid and pharyngeal regions, or from below and to one side by a lateral pharyngeal and spheno-palatine route. By the *intracranial* procedure it has been approached from above through a median opening in the cranial vault, or from the side by an opening in the temporal region with elevation of the subjacent lobe. Mere statements of their performance are all that we possess of the earlier experiments. Thus in a discussion of the paper by Tiedeman and Mass in 1900, Koenig[2] states that Julius v. Michel in 1881 attempted, by a frontal approach, to remove the gland from a number of dogs, cats and rabbits. Most of the animals were lost owing to immediate operative complications, but some survived for long periods.

Sir Victor Horsley was apparently the first to publish a personal note regarding the experimental removal of the gland. In an article[3] dealing largely with the functions of the thyroid a brief statement is made to the effect that he had removed the pituitary body from 2 dogs, which were sacrificed at the end of 5 and 6 months, respectively, and that the hypophysectomy led to no disturbing symptoms. No details are given beyond the fact that the motor cortex was found to be exceptionally excitable in both animals. This casual statement doubtless was given wider circulation than its distinguished author anticipated.

The first actual contribution to the subject was made in 1892 by Marienesco,[4] who had been associated with Marie in the earlier study of acromegaly. In his brief article he mentions (without reference) some experiments of Dastre's undertaken 3 years previously, in which the gland was approached through the mouth: the animals all succumbed. Marienesco's operations, also conducted by the buccal route, were made upon 8 cats. In his procedure the soft palate was divided, the base of the skull under the sella turcica was trephined and the hypophysis, so far as possible, destroyed with a cautery. Three of these 8 animals survived the operation and lived, respectively, 3, 5 and 18 days. In the interim they lost flesh rapidly in spite of forced feeding, and acquired a subnormal temperature. There was no post-mortem evidence of infection or hæmorrhage: the hypophysis on gross examination was absent, but there was no microscopical confirmation of the apparent complete destruction of the gland. Marienesco concluded that loss of the gland is compatible with life for some weeks.

Gley, whose important contributions to our knowledge of the cervical glands are well known, in 1892 reported a single experiment on the hypophysis of a thyroidectomized rabbit.[5] Through a trephine opening in the mid-cranial vault an instrument was introduced through the cerebrum into the sella turcica and an attempt made to destroy the gland in this blind fashion, with most unsatisfactory and inconclusive results.

The first studies which include any suggestive observations on the symptomatology of apituitarism were published in 1892 and 1894 by Vassale and Sacchi.[6] By an operative approach differing only in a few minor details from that employed by Marienesco an attempt was made to destroy the gland by the use of the thermo-cautery and chromic acid. All but 18 of the 23 dogs and 17 cats that were used succumbed to operative complications of hæmorrhage or infection. Of the animals which escaped these complications the greater number died during the first week, the longest survival being 14 days, and it was found that the gland in this animal had not been entirely destroyed. The total removal of the gland, therefore, regardless of operative complications, was regarded as necessarily fatal.

Their later report included a description of the 1 dog which had survived a supposedly complete removal for 37 days and another a partial removal for over a year. In the latter case a fragment of anterior lobe was obviously present, but no microscopic examination of the base of the brain seems to have been made in the cases in which naked-eye appearances made it seem probable that the extirpation had been complete.

The symptoms which were observed in the fatal cases were psychic depression, apathy, motor disturbances in the shape of fibrillary and irregular muscular movements, lowering of temperature, polydipsia, anorexia, loss of weight and ultimate

[2] *Berl. klin. Wchnschr.*, 1900, XXXVII, 1040.

[3] Functional nervous disorders due to loss of thyroid gland and pituitary body. Abstract of third Brown Lecture. *Lancet*, 1886, I, 5.

[4] M. G. Marienesco: De la destruction de la glande pituitaire chez le chat. *Compt. rend. Soc. de Biol.*, 1892, IV, N. S. 509-510.

[5] E. Gley: Recherches sur la function de la glande thyroide. *Arch. de physiol. norm. et path.*, 1892, IV, 311-326.

[6] Sulla distruzione della ghiandola pituitaria. *Riv. sper. di Freniat. Reggio-Emilia*, 1892, XVIII, 525-561.

Ulteriori esperienze sulla ghiandola pituitaria. *Ibid.*, 1894, XX, 83-88. Also Atti d. XI Cong. med. internaz. Roma, 1904. *Il Patol. gen.*, 163-165.

coma; less constant symptoms were rigidity of the hind-legs, curvation of the spine, convulsions, vomiting and polyuria. The authors concluded that the hypophysis was of great physiological importance; that its loss was incompatible with life and that, like the thyroid, it produced a secretion, in the absence of which a fatal autointoxication might occur.

Gatta, in 1896,[7] by a buccal procedure similar to that employed by Vassale and Sacchi, attempted to destroy the hypophysis in 4 cats after a primary thyroidectomy. Death occurred in from 8 to 18 days, preceded by a failure of general nutrition and lowering of temperature, albuminuria and rigidity of the hind-legs. There was no microscopical control, but the author concluded that the hypophysis was essential to the maintenance of life.

In the following year (1897), after some similarly incomplete experiments carried out by the buccal route with an additional temporary tracheotomy, Biedl [8] reached the opposite conclusion, namely, that the gland is not vitally important. Pineles [9] makes brief mention, likewise, of a number of attempted buccal extirpations on cats undertaken in the Physiological Institute in Vienna, in which the results were entirely negative, as only 2 of the animals survived, and a subsequent examination showed that the removal had been incomplete.

At this time Cyon, in a series of articles in Pflüger's Archives (1898-1900),[10] advanced his well known views in regard to the supposed function of the hypophysis in regulating intracranial blood pressure. In the course of these experiments he exposed the gland and stimulated it (mechanically and electrically), and thought that he obtained results similar to those produced by vagal stimulation, whereas its total destruction was regarded as equivalent in effect to section of these nerves. These views have not received corroboration, and, as will be seen later, such manipulations as are necessary for the total removal of the canine gland, may be carried out with no effect whatsoever upon blood pressure or pulse rate, as shown by a kymographic tracing kept during the course of the surgical procedure. Cyon's operations were limited to rabbits and were not conducted with the view of obtaining recoveries.

In 1898 and later, elaborate studies were made by Arnold Caselli [11] with the primary object of determining the functional interrelation between the hypophysis, thyroid and parathyroids. He was led to believe in an antagonistic relation between these structures, for parathyroidectomized animals were thought not to show tetany if the hypophysis was removed at the same time, and further, that tetany due to loss of the parathyroids would be checked by a prompt hypophysectomy. In the course of his experiments he removed the hypophyses from a number of frogs by a pharyngeal route, without eliciting any particular subsequent disturbance, though in a few cases there occurred tetanic or epileptoid symptoms comparable to those which were found to follow intracranial operations of other kinds on these same animals. The author makes no mention of post-mortem examinations or microscopical studies.

He operated likewise upon a series of rabbits by the buccal route, without success, owing to inevitable meningitis; and almost equally unsatisfactory were his later operations on dogs and cats. By a most difficult and complicated spheno-palatine approach he operated on a series of 19 animals, almost all of which promptly succumbed to operative complications. In a second series of 36 canine operations he adopted the buccal approach of Vassale and Sacchi. Only 3 of the cases in which infection could be excluded were presumed, from naked-eye appearances, to be total removals, and the animals lived 16, 21 and 22 days, respectively, showing symptoms similar to those recorded by Vassale and Sacchi.

In the partial removals he observed transient phenomena of a similar nature with subsequent restoration to a subnormal state not incompatible with life. In 1 puppy there was an arrest of development, as shown by a comparison of weight with a control animal. Despite the uncertainty of his operative results, Caselli ventured to accept Vassali's opinion that the gland was of physiological importance, it being necessary for normal development and its total loss being followed by autotoxic disturbances leading to coma not unlike that which may occur in diabetes.

The results of experiments conducted on similar lines were published in 1900 by Friedmann and Maas.[12] On gross examination it was found that 13 of their 18 animals had presumably been subjected to a complete hypophysectomy (no microscopic control). Six of the animals succumbed to operative complications of infection and hæmorrhage. Five of the survivers died at periods of from 2 to 38 days after the operation, no cause for death being found, though infection was considered probable. One animal was sacrificed after 3½ months and there was no macroscopic evidence of remaining glandular tissue. The authors concluded that the hypophysis is not essential to life, and in a later paper (1902) Friedmann [13] emphasizes this opinion and denies the retarding influence upon growth due to the loss of the gland which Caselli had described.

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[7] Gatta: Sulla distruzione della ghiandola pituitaria e tiroide. *Gazz. d. osp.* 1896, N. 146, 1537.

[8] Biedl. (Discussion) *Wien. klin. Wchnschr.*, 1897, X, 196.

[9] F. Pineles: Die Beziehungen der Acromegalie zum Myxödem, etc. *Samml. klin. Vortr.*, Leipz., 1899, N. F. 242, 1423.

[10] A. von Cyon: Beiträge zur Physiologie der Schilddrüse und des Herzens. *Pflüger's Arch. f. ges. Physiol.*, 1898, LXX, 127-521. Die Verrichtungen der Hypophyse. *Ibid.*, 1898, LXXI, 431; LXXII, 635; LXXIII, 483; LXXIV, 42, 97; 1899, LXXVII, 215; 1900, LXXXI, 267.

[11] Caselli: *Pflüger's Arch. f. ges. Physiol.*, 1898, LXXIII, 385.

Studi anat. e sperim. sulla fisiopatologia della ghiandola pituitaria. *Reggio nell' Emilia, Tipogr. Calderini*, 1900.

Influenza della funzioni dell' ipofisi sullo sviluppo dell' organismo: nota preventiva sulla fisiopatologia della ghiandola pituitaria. *Riv. sper. di Freniat., Reggio-Emilia*, 1900, XXVI, 176, *Ibid.*, 1900, XXVI, 486.

Étude anatomique et physiologique de la glande pituitaire. *Bull. Soc. de méd. de Gand.*, 1901, LXVIII, 311-313.

[12] Friedmann and Maas: Ueber Extirpation der Hypophysis Cerebri. *Berl. klin. Wchnschr.*, 1900, XXXVII, Nr. 52, 1213-1215.

[13] Friedmann: Noch einige Erfahrungen über Extirpation der Hypophysis Cerebri. *Berl. klin. Wchnschr.*, 1902, XXXIX, 436-438.

Lomonaco and Van Rynberk in 1901 [14] reported certain experiments performed on dogs and cats by an operation through the cranial vault similar to that employed by Gley, with an attempt to destroy the hypophysis by a needle introduced directly through the cerebrum. Though in only a small proportion of the cases was the gland apparently destroyed, the authors nevertheless concluded that it is not essential to life and that the unfavorable results of hypophyseal experiments were due to inevitable injury of important portions of the neighboring cerebrum.

Similar conclusions were reached by Gaglio in 1900 and 1902 [15] as a result of operations carried out upon frogs and toads by a buccal method. In the 2 frogs which survived from 1 to 3 months the removal of the gland appeared to be complete, but no microscopic examination was made. The main object of his research was to test the hypotheses of Cyon, with which he disagreed.

Pirrone in 1903 [16] reported his attempts to remove the canine gland by the spheno-palatine route which had been so unsuccessful in Caselli's hands. In view of the difficulties and uncertainties of this procedure he naturally attributed many of the post-operative phenomena to trauma rather than to loss of the gland, these phenomena consisting chiefly of variations in pulse, temperature and respiration. He nevertheless observed in 6 of his cases symptoms which we recognize to-day as manifestations of apituitarism—the characteristic depression, rigidity of the extremities with spastic gait, curvation of the spine and fibrillary twitchings, leading to cachexia and death. His conclusions were: (1) that all the phenomena consecutive upon hypophysectomy should not be attributed to disturbance of the function of the pituitary gland; (2) that absence of hypophyseal function accounts for the disturbance of motility, the psychic depression, the rapid emaciation, cachexia and death; (3) that the cardio-vascular, respiratory and thermic phenomena are the consequences of operative traumatism: (4) that removal of the hypophysis does not modify the composition of the urine; (5) that although the mechanism of hypophyseal function is not at all well understood one may say nevertheless that the gland is of vital importance; for, whereas a partial lesion of the organ may be compatible with life, its total removal leads to death.

Out of a series of 25 canine operations reported in 1903-1904,[17] Dalla Vedova, like most of his predecessors, lost a majority (21) of the animals from operative complications. Two of the survivers were sacrificed at a late period, and no macroscopic traces of the gland were present. Microscopic studies were not made as controls, an omission which the author himself notes; and in his second paper he calls attention to the fact that in the 2 survivors of his series originally reported as "totals" the microscope had revealed notable traces of remaining glandular tissue. His original conclusions, therefore, that animals might survive after a total hypophysectomy, were reversed in his second paper.

Brief mention was made in 1904 by Eiselsberg [18] of the fact that in an effort to reproduce acromegaly he had extirpated the hypophysis from a number of kittens by a buccal operation. One of the animals lived 10 days, but the others succumbed soon after the operation, supposedly from the immediate effects of the surgical procedure.

Fichera, in 1905,[19] reported the results of operations on 40 chickens, conducted by a retropharyngeal route through an incision in the hyoid region. The incision was made alongside of the pharynx without opening its cavity, thus lessening the danger of infection, and the attempt was made to destroy the gland with a cautery. In his 40 cases there were 29 recoveries, the greater number of which were sacrificed after some months. Four of these were regarded as microscopically complete removals. No constant or characteristic symptoms were noted and the author concluded that in chickens the hypophysis is not essential to life, though its complete removal may retard development.

By far the most important contribution to the subject was made in 1908 by Paulesco of Bucharest.[20] After some fruitless preliminary attempts 10 years previously to reach the dog's hypophysis by a buccal route, this physiologist, in collaboration with a surgeon (Balacesco), evolved an intracranial method of approaching the gland by the temporal route, applying what has of late years come to be a new principle for operations within the skull—namely, cerebral dislocation for the purpose of exposing parts otherwise inaccessible. In Paulesco's procedure both temporal muscles were detached from the skull and reflected downwards, permitting the establishment of a generous bilateral opening both in bone and dura. This made it possible to introduce an elevator under one temporal lobe, and to lift the brain sufficiently to expose the dangling pituitary body without cerebral injury or compression, owing to the accompanying dislocation and protrusion of the opposite hemisphere through its overlying bone defect. It can be readily understood that this operation, though complicated and delicate, represented a notable improvement over all the earlier ones, in view of the excellent exposure of the gland which it permitted and the lessening at the same time of the risks of infection which had been such a drawback to the buccal procedures.

In Paulesco's long series of hypophysectomies, 24 proved to

[14] D. Lomonaco and Van R. Rynberk: Richerche sulla funzione della ipofisi cerebrale. *Riv. mens. di neuropat. e psichiat.*, March and April, 1901, No. 9, p. 2.

[15] Gaglio: Recherches sur la function de l'hypophyse du cerveau chez les grenouilles. *Arch. ital. de biol.*, 1902, XXXVIII, 177-187.

[16] Pirrone: Contributo sperimentale allo studio della funzione dell' ipofisi. *Riforma med.*, 1903, XIX, No. 7 and 8, 169-175, 205-209.

[17] Dalla Vedova: Per la funzione dell ipofisi; nota preliminaria. *Boll. r. Accad. Med. di Roma*, 1903, XXIX, 150-160.

Per la funzione dell' ipofisi cerebrale; nota seconda. *Ibid.*, 1904, XXX, 137.

[18] v. Eiselsberg: (Discussion) *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1904, XXXIII (Kleinere Mittheil.), 111.

[19] G. Fichera: Sulla distruzione dell' ipofisi. *Sperimentale. Arch. di Biol. norm. e patol.*, 1905, LIX, 739-796.

[20] N. C. Paulesco: L'Hypophyse du Cerveau. Vigot Frères, Eds. Paris, 1908.

be *total*, the average duration of life of all cases being 24 hours. He made a second grouping of 7 *partial* hypophysectomies, comprising those cases which at operation were supposed to be total, but which the microscope subsequently showed to be incomplete. He formed the opinion that animals may live for a longer or shorter time according to the size and vitality of the remaining glandular fragment: two of the partially hypophysectomized animals survived for 5 months and a year respectively without exhibiting any observable deviation from the normal.

Removal of the *anterior lobe alone* (7 cases) he found to be equivalent to removal of the entire gland: loss of the *posterior lobe* (5 cases) led to no appreciable disturbance whatsoever: and separation of the *hypophyseal stalk* (6 cases) from the base of the brain amounted to a complete or to a nearly complete removal, as the case might be.

Paulesco's experiments were carefully controlled by performing the customary manipulations without the final step of removal of the gland, showing that the fatalities were not due to the opening of the third ventricle or to other cerebral lesions brought about by the surgical procedure. Careful post-mortem histologic studies of the base of the brain and contents of the sella turcica were made in all cases. In view of the importance of this contribution, his final conclusions may be given in his own words:

L'hypophysectomie totale est suivie, à bref délai, de la mort de l'animal. La durée moyenne de la survie, chez le chien, est de 24 heures.

Quand la survie est plus longue (elle peut même être indéfinie), c'est que des débris de la portion épithéliale de l'hypophyse (parfois minimes et même microscopiques) ont échappé à la destruction et sont demeurés vivaces,—ainsi qu'il arrive dane ce que nous avons appelé l'hypophysectomie presque totale.

L'insuffisance du fonctionnement de l'hypophyse, à la suite de l'hypophysectomie totale ou presque totale, *ne se manifeste par aucun symptôme particulier et caractéristique*,[21]—et, dans les cas de survie prolongée, il ne se produit aucun trouble trophique appréciable au niveau des extrémités (muceau, membres). . . . .

En résumé, l'hypophyse est un organe indispensable à la vie, son absence étant rapidement mortelle.

Des diverses parties qui la constituent, la plus importante, au point de vue fonctionnel, est la couche corticale du lobe épithélial.

A few months after Paulesco's publication (1901) Gemelli[22] made record of a series of feline buccal operations by a method similar to the original procedure of Vassale and Sacchi. Eight of the animals survived and were sacrificed at periods varying from 6 months to a year. Of these, 7 were shown by most careful microscopic examination of the base of the brain and the sella turcica (decalcification) to have been subjected to a complete hypophysectomy. In one of the animals a certain amount of pars intermedia was found containing many small colloid vesicles. No especial symptoms were noted, with the exception of polyuria and polydipsia through the first few days and a subnormal temperature for the first 24 hours. Gemelli concludes therefore—Paulesco's observations to the contrary—that the gland is not essential to life, but that it possesses a certain compensatory function, the anterior lobe having some antitoxic properties and the posterior lobe some influence upon renal secretion. These studies of Gemelli's we have repeated, with results which will be given in a later paragraph.

Livon (1909)[23] performed a number of operations by the temporal route, making the serious surgical omission of not opening both sides of the skull. His primary object was to investigate the excitability of the hypophysis to various stimuli; but a few supposedly complete removals were saved for observation, the average duration of life in these animals being 36 hours. The author concludes that the hypophysis is a vital organ and that, contrary to Cyon's belief, it is not directly excitable and is not an autoregulator of the circulation through its sensibility to pressure.

In the same year (1909) from this laboratory, Reford and Cushing[24] reported a series of 20 operations also conducted on the lines similar to those laid down by Paulesco. The results of these observations were regarded as confirmatory of his main contention that total loss of the gland in the canine is incompatible with life. There were no microscopic controls.

### III. Analysis of these Earlier Investigations.

For the convenience of reference, the methods employed in these several investigations, together with their results, have been gathered in tabular form. As can be seen, there has been an even division of opinion in regard to the gland's importance, and in view of the methods used in conducting the researches, it is perhaps remarkable that any of the observers, before Paulesco, came to the conclusion that the structure is actually essential to life. Table I shows at a glance how rarely have been observed the two most important elements for the success of these studies—(1) an operative method which assures, with reasonable certainty, totality of removal without complicating cerebral injury, hæmorrhage or infection, and (2) a subsequent microscopic corroboration of its accomplishment.

By the trans-cerebral operation attempted by Gley and Lomonaco an assured destruction of the gland is, of course, an impossibility, and the unavoidable damage to the nervous system by such a procedure would, in any event, have confused hypophyseal symptoms beyond recognition. In the difficult sphenopalatine procedure introduced by Caselli, infections were almost inevitable, and after 19 attempts Caselli himself abandoned the method in favor of the buccal route of Vassale, which he modified in some respects. Pirrone's results were possibly less unsatisfactory, but it is evident from his description that traumatism played a large part in them.

The buccal route, as can be seen, has been the favorite one,

[21] Italics, ours.

[22] Gemelli: Ulteriore contributo alla fisiologia dell' ipofisi. *Sonderabdruch aus Folia neurobiologica*, 1908, II, E. Hekma, Groningen. Also; Sur la fonction de l'hypophyse. *Arch. ital. de biol.*, 1908, L, 157-174.

[23] Ch. Livon: L'hypophyse est-elle un centre réflexe circulatoire? *Marseille méd.*, 1908, XLV, 745.

[24] Reford and Cushing: Is the pituitary gland essential to the maintenance of life? *Johns Hopkins Hosp. Bull.*, 1909, XX, 105.

TABLE I.—RESULTS OF PREVIOUS INVESTIGATIONS.

| Author. | Route. | Subject. | Successful total removals. | Microscopic confirmation. | Importance to life and its duration after removal. | Symptoms in fatal cases due to apituitarism. | Symptoms of hypopituitarism in long survivals. | Operative complications. |
|---|---|---|---|---|---|---|---|---|
| 1 Michel .....1881 | Frontal. | Dogs, cats, rabbits. | (?) | ..... | ..... | ..... | ..... | ..... |
| 2 Horsley .....1886 | (?) | 2 dogs. | 2 (?) | Omitted. | Not essential; 5-6 months. | ..... | None observed. | ..... |
| 3 Dastre .....1889 | Buccal. | ..... | ..... | ..... | ..... | ..... | ..... | No operative recoveries. |
| 4 Marienesco .....1892 | Buccal. | 8 cats. | (?) | Omitted. | Three survivals; for 4, 5, 18 days. | Possibly observed; cf. emaciation and lowered temperature. | ..... | ..... |
| 5 Gley .....1892 | Cranial vault. | 1 rabbit. | ..... | Partial destruction. | ..... | ..... | ..... | ..... |
| 6 Vassale and Sacchi....1894 | Buccal. | 23 dogs, 17 cats. | 15 (?) | In one case. | Important and essential to life; 37 days in one case. | Evidently observed; clearly described. | Evidences of insufficiency. | Many complications. |
| 7 Gatta .....1896 | Buccal. | 4 cats. | 4 (?) | Omitted. | Essential. | Possibly observed. | ..... | ..... |
| 8 Biedl .....1897 | Buccal. | Cats. | (?) | Omitted. | Not essential; survivals 8-18 days. | ..... | ..... | ..... |
| 9 Caselli .....1900 | a. Buccal. | Rabbits. | ..... | ..... | ..... | ..... | ..... | Unsuccessful. |
| | b. Spheno-palatine. | 19 dogs and cats. | ..... | ..... | ..... | ..... | ..... | Unsuccessful. |
| | c. Buccal. | 28 dogs. | 3 (?) | Occasionally made. | Essential; survivals 16, 21, 22 days. | Evidently observed but confused by complications. | Recovery after transient symptoms; arrest of development. | Many infections; meningitis. |
| 10 Friedmann and Maas..1900 | Buccal. | 18 cats. | 13 (?) | Omitted. | Not essential; 3½ months. | Denied; deaths attributed to infection. | Growth retardation denied. | Fatal complications frequent. |
| 11 Lomonaco Rynberk....1901 | Cranial vault. | 49 dogs and cats. | 4 (?) | Omitted. | Not essential; 20 days. | Denied; deaths attributed to cerebral injuries. | ..... | Cerebral injuries. |
| 12 Gaglio .....1902 | Buccal. | Frogs, toads. | 2 (?) | Omitted. | Not essential; 47 and 95 days. | ..... | ..... | Infections and paralyses. |
| 13 Pirrone .....1903 | Spheno-palatine. | Dogs. | 6 (?) | Omitted. | Essential; 7-15 days. | Probably observed but confused from complications. | Recovery after transient symptoms. | Cerebral injuries; inconclusive. |
| 14 Dalla Vedova.....1903 | Buccal. | 25 dogs. | 4 (?) | Omitted. | Not essential. | ..... | ..... | Operative complications in 84 per cent; 4 hæmorrhages; 11 infections. |
| Dalla Vedova.....1904 | ..... | ..... | ..... | Based on two survivals of 1903 series. | Probably essential. | ..... | Gain in weight in one case; not commented on. | ..... |
| 15 Fichera .....1905 | Lateral pharyngeal. | 40 chickens. | 11 (?) | Made in four cases but not described. | Not essential. | ..... | Retarded development. (?) | 27 per cent operative deaths. |
| 16 Paulesco .....1908 | Temporal fossa. | 52 dogs and cats. | 24 | Made. | Essential; 2 days. Fragments of gland found in all longer survivals. | Fully observed and described. | Recovery after transient symptoms of cachexia hypophyseopriva; gain in weight (not commented on). | Occasional cerebral injury. |
| 17 Gemelli .....1906 and 1908 | Buccal. | Cats. | 7 | Made. | Not essential; 6-12 months. | ..... | Transient symptoms for few days. | Meningitis, frequent. |
| 18 Livon .....1909 | Temporal fossa. | 39 dogs. | Few. | Omitted. (?) | Essential; 36 hours. | Observed. (?) | ..... | ..... |
| 19 Reford and Cushing...1909 | Temporal fossa. | 20 dogs. | 15 (?) | Omitted. | Essential; 24-48 hours. | Observed and described. | Recovery after transient symptoms, with naked-eye fragments remaining. | Occasional hæmorrhage. |

having been employed in 11 out of the 19 researches, and yet all the authors have acknowledged the frequency of complications from hæmorrhage and infection which attend the procedure, and in many of the earlier experiments, as those of Marienesco and Vassale, the cautery was resorted to as the uncertain means of destroying the gland. The reports of this method which deserve chief mention, as they include the greater number of presumably successful experiments, are those of Vassale, Caselli, Dalla Vedova and Gemelli.

The two former evidently described symptoms of fatal cachexia hypophyseopriva due to loss of the gland, and though the evidence does not seem in all cases particularly conclusive, they regarded the structure as physiologically important and possibly essential to life. Survivals for as long periods as they observed them, in the light of our present knowledge make it seem probable, particularly in the absence of microscopic controls, that the extirpations were incomplete, unless possibly very young animals were used. For example, in the 28 dogs of Caselli's later series, 7 of the 14 regarded as total removals succumbed to meningitis, 2 to hæmorrhage, 1 to the anæsthetic, and 1 to enteritis, leaving only 3 in which operative complications could be excluded, and these 3 survived for the unusually long periods of 6, 21 and 22 days, respectively. Of his 6 supposedly total feline removals there were 5 deaths from meningitis. Although it is apparent that definite hypophyseal symptoms were observed by Caselli as well as by Vassale, the clinical picture was too greatly confused by the frequency of operative complications to make their deductions at all convincing.

The experience of Dalla Vedova is illuminating, inasmuch as he was led to reverse his earlier statement to the effect that the gland was not physiologically essential. This conclusion he had based on the 4 survivals in his series of presumably total removals, but subsequent careful histological studies demonstrated the presence of remaining anterior lobe fragments in each of these animals Gemelli alone of these 4 observers concluded, from his series of feline buccal operations, that the gland is not essential. To this we will refer later.

It can be seen that only 4 of Paulesco's 15 predecessors in this work regarded the gland as important or essential having observed symptoms which we now recognize as being definitely attributable to loss of the gland, rather than to the surgical manipulations at the base of the brain or to secondary operative complications. In only 3 of the investigations had there been an attempt made to control the result by microscopic studies, and of these 3, Fichera alone concluded that the gland was unimportant. His work was done on fowls by a difficult approach which necessitated destruction of the gland by a cautery. No detailed description evidencing the thoroughness of the histological studies is given, and as he observed retarded development, as we have in our animals after "nearly total" removal, the suspicion is aroused that fragments of the anterior lobe must have remained. However, we have had no experience with the avian hypophysis, and until his experiments are repeated Fichera's claims must stand uncriticized.

It will be noted that Paulesco is the only author who had a large number (24) of successful extirpations which were controlled by histological studies. Even with the operation which he introduced, allowing clear exposure of the gland and permitting accurate manipulations, his microscopic examinations showed that in all permanent recoveries fragments of the gland had been left, even when at operation the enucleation had been supposedly complete. Thus Dalla Vedova's earlier demonstration that even minute fragments of the gland might support life received further confirmation. Paulesco's argument is most convincing and his main contentions have already been in a measure confirmed by 2 subsequent (confessedly incomplete) reports—one by Livon and one from this laboratory by Reford and Cushing—in both of which his operative method was followed in the main.

As Gemelli's later paper was published with full knowledge of Paulesco's results, which they directly controvert, and as his buccal operations were well executed and microscopically controlled, his results deserve especial consideration, but we have been unable to confirm them, as will be seen.

Although our chief interest has come to be centered in the altered physical condition of the animals surviving for long periods after a purposeful partial hypophysectomy—an aspect of the subject heretofore neglected—it has seemed nevertheless of paramount importance to finally settle this debated question of essentiality of the gland, and hence the first part of our personal report, after a full description of the canine operation of Paulesco, will be devoted to this subject-matter.

## IV. The Surgical Procedure.

1. *Paulesco's Temporal Route.*—Regarding this method as the most consistently successful of any heretofore employed and particularly suitable for an approach to the canine hypophysis, a procedure was evolved based on the principles introduced by Paulesco and meeting at the same time our personal requirements. This we have used without variation in our series of over 100 cases.

The canine hypophysis lies in a shallow sella turcica, less closely embraced by the local pocket of dura in which it rests than is the case with many other mammals. Hence with proper elevation of the temporal lobe the structure becomes accessible from its lateral aspect. This anatomical characteristic of the gland does not hold true for the cat or rabbit, for in both of these animals it occupies a deep meningeal pouch, the walls of which are channeled by sinuses, the chance injury to which would render further clean-cut manipulations impossible. Indeed, owing to a similar anatomical arrangement, the gland is far less accessible in old than in young dogs, and it was this fact which led us, in spite of their smaller size, to prefer young animals for purely surgical reasons—a matter which proved to be of importance, as we shall see.

The dog's skull possesses a broad temporal exposure which allows of fairly easy access to the inferior surface of the temporal lobe and hence to the sella turcica, but an attempt to elevate this lobe sufficiently to gain a clear view of the structure concerned leads inevitably to cortical injury, bleeding and operative confusion at the outset. In the presence of a large contralateral opening in bone and dura, however, the opposite

hemisphere will protrude sufficiently to allow the temporal lobe on the side of the approach to be lifted without risk of local cortical damage or of producing general cerebral compression. This is the principle of cerebral dislocation.

The age of the animal is of importance in other respects than mere enucleability of the hypophysis, for in young dogs all the steps of the operation are more easily performed. The temporal muscle is more readily separated from the bone, the cranial diploic sinuses are undeveloped so that in making the bone defects less blood is lost, and the dura is much less adherent and friable. For a long and delicate operation these things combine to permit a shorter and dryer operation with a better ultimate exposure of the gland. The difference in results of operations performed on old and young animals will be alluded to later.

In all of our canine operations we have followed a surgical technique, the exact counterpart of that which would be applied to intracranial operations on human beings. This implies skillful anæsthetization, a complete surgical equipment, proper sterilization of supplies and instruments, the wearing of gowns and gloves by the operator and assistants—indeed all that goes to make an operation safe and the possibility of infection remote (Fig. 1). Ample surgical experience, too, especially in so far as it relates to the tricks of controlling hæmorrhage and avoiding cerebral injury in intracranial work is desirable; for, owing to difficulties from the small canine field of operation, the surgical risks on this score are greater than would be the case with man.

In our earlier cases we had an occasional wound infection involving skin or muscle layers, but never a fatal meningitis. In the last 70 or 80 operations healing has taken place by primary union, and in the occasional early death of a totally hypophysectomized adult there were no evidences of infection. In our earlier experiences likewise, animals (not included in the series), particularly old adults, were not infrequently lost owing to uncontrolled hæmorrhage from vessels in the neighborhood of the hypophysis—meningeal, cavernous sinus or carotid. This accident, even in our later series, has occasionally led to the abandonment of the operation and the sacrifice of the animal under the anæsthetic, but complications from hæmorrhage have become of rare occurrence since we have become sufficiently familiar with the steps of the procedure.

From the beginning the greatest care has been exercised in the avoidance of any possible injury to the brain. This object has been attained, partly through the employment of the rounded spatula used for the temporal lobe elevation and partly owing to the contralateral cranial opening which permits of dislocation. Though Paulesco introduced the bilateral craniectomy for this purpose, he does not clearly state whether the dura is to be opened on both sides or only on the side of the approach. The efficiency of the dislocation is immensely increased by the doubly opened dura, and in fact there is no particular advantage in the additional cranial opening if the dura is left intact, as Paulesco must have learned. Livon, however, attempted his temporal operations with a unilateral opening.

Of the few special instruments which are useful (Fig. 2), a proper elevator is possibly the most essential. The form we have devised is about 1 cm. in width; it is slightly flexible so that it may be bent to fit beneath the temporal lobe, and the surface which is applied to the cortex is convex ("spoon-backed") from side to side, the edges and tip being rounded off. This rounding not only prevents the edges of the retractor from injuring pia-arachnoid and contusing the brain, in which case the soft cerebral substance, under pressure, extrudes about the instrument and obstructs the view, but also affords a channel of approach which is circular on cross section instead of semicircular and thus doubles the space for the operator's vision, necessarily restricted at best. A delicate hook-knife for the purpose of slitting the dura from within outward when making the incision deep in the temporal fossa, is useful and obviates the danger of cutting or injuring cortical vessels should the membrane be otherwise incised. The instruments used for the hypophyseal manipulations themselves are simply a pair of delicate strong forceps, bent in the middle so as to allow the operator to see along the blades, and a light spoon curette, which is useful when the posterior lobe alone is to be removed.

With the excellent view obtained by this operative method the gland, in the majority of cases, may be extirpated accurately and completely, or the delicate manipulations of partial removal may be performed with reasonable certainty. Whatever procedure may have been attempted, however, and presumably carried out, past experience has shown the necessity in all cases of a subsequent thorough post-mortem microscopic confirmation of its success. In the first report from this laboratory (Reford and Cushing) naked-eye appearances alone were relied upon. In the earlier cases of our present series, histological studies were made only when there was a reasonable doubt of totality, but we have come to regard it necessary to make serial sections in all cases.[25]

2. *The Operation.*—The animal should be weighed, its age estimated if not known, and preceding the operation it should be placed for a day or two in a metabolism cage so that the urinary output can be estimated and the standard amount of food and

[25] Great care must be taken at the autopsy to remove the brain without dislocating from the infundibular region any of the adherent blood-clot or possible fragment of gland which may have been overlooked at the operation. The routine performance has been conducted as follows: After reopening the incision and reflecting the temporal muscles the remainder of the calvarium is removed and the dura freely opened. The olfactory lobes are then scraped out of their pockets and the anterior portion of the brain lifted until the optic nerves come into view. They are divided as in the usual method of removing the brain of man. This brings into view the carotid arteries and hypophyseal region, and especial care must be exercised not to tear away the infundibular stalk from the tissue which may still occupy the sella turcica. All of this tissue is carefully freed from the bony floor, and still adherent to the base of the brain is removed intact with this entire structure. A block of tissue is then cut from the base of the brain including the optic chiasm and the entire infundibular region, and fixed in Zenker's or Bensley's fluid. The tissue is eventually embedded in paraffin and serial sections made and variously stained. The entire series of ductless glands, needless to say, is similarly removed and blocks preserved for histological study.

FIG. 1.—Showing general arrangement of field of operation. Operator wearing head-light.

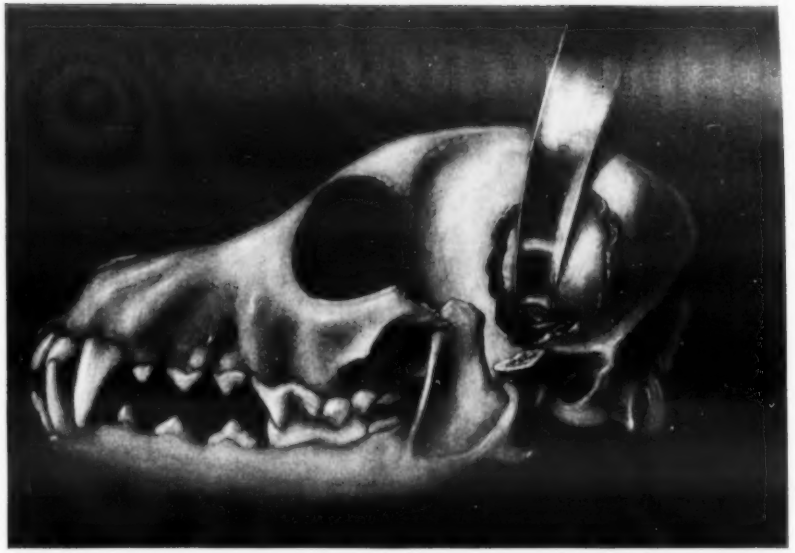

FIG. 4.—Drawing to show lateral defect, small dural incision and landmarks of gland in left lateral subtemporal approach. Tip of curved spatula enters between internal carotid and third nerve with gland in view.

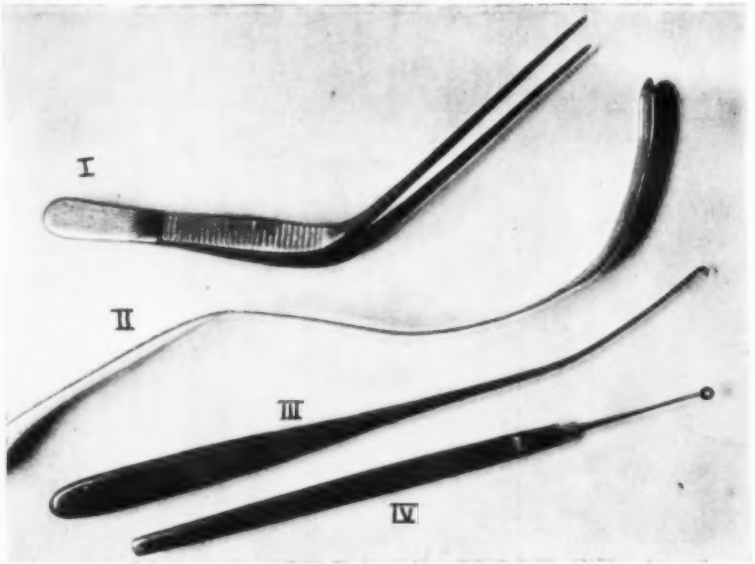


FIG. 2.—The few special instruments found useful (reduced one-third). I. Forceps for liberating gland from bed and picking it out by stalk. II. Spatula with spoon-shaped end for elevation of temporal lobe. III. Special cutting hook for deep incision in dura. IV. Spoon useful for removal of fragments or for dislocation of posterior lobe.

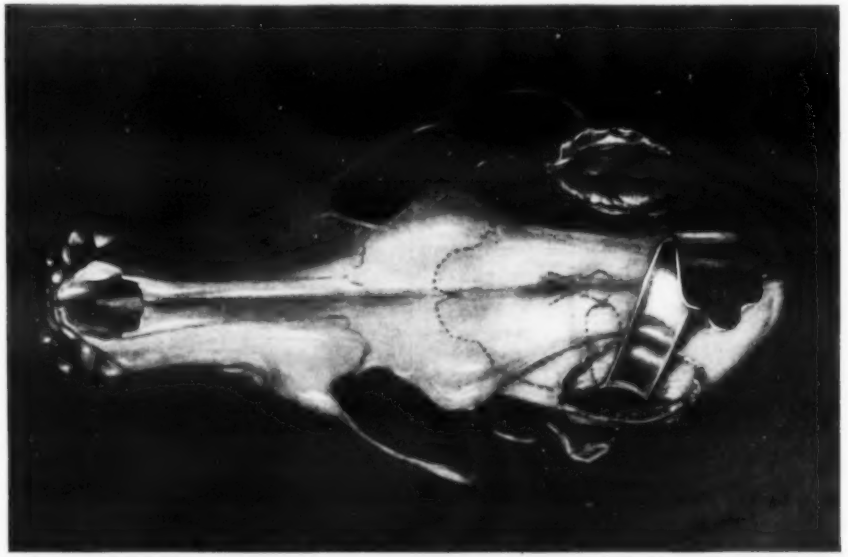

FIG. 5.—Contrast with Fig. 4. Upper view. Curved spatula in place, elevating temporal lobe. Note dislocation outward of right hemisphere through defect in bone and dura.

water regulated. After administering morphine from a quarter to half an hour before the operation, the drowsy animal is placed, belly down, on the operating table, with the head raised upon a wooden block hollowed out to fit the jaws. After securing the tips of the ears under the chin the scalp is carefully shaved from a point just behind the eyebrows well down upon the neck and out upon the ears on both sides (Fig. 3). Too energetic scrubbing is inadvisable: green soap, alcohol and bichloride solution suffice for the final preparation after anæsthesia (ether) has been administered. A piece of gauze wet in bichloride is then laid over the head. Dry sterile towels are spread over this and pinned to the skin in such a way as to leave only a narrow linear slit, through which gauze and skin are incised.

FIG. 3.—(Forty-eight hours after operation.) To show extent of shaved area and usual appearance of undressed wound before removal of sutures.

The layer of superficial muscles attached to the median cranial ridge are divided in the mid-line as far as the occipital crest, at which point the incision diverges in a Y as it passes down upon the neck. Concentric with, but about 5 mm. within, the upper line of insertion of the exposed temporal muscles (in order to leave sufficient margin for subsequent suture) an incision is made through the muscles, extending from a point near the orbit and ending at their posterior and inferior point of attachment, where a small artery is encountered. With a sharp elevator the temporal muscles and periosteum are then stripped downwards from their cranial attachments.

On the side chosen for the approach (we have invariably used the left: Figs. 4 and 5) it is necessary to strip the muscle far enough down to give access to the posterior zygomatic attachment. The zygomatic arch is then scraped in a forward direction until free from its muscular attachments, when it is divided with bone forceps, the arch broken as far forward as possible and the fragment dissected out of its bed. As is true of the Gasserian ganglion operation in man, this is an important step, for it permits of sufficient downward retraction of the thick muscle to assure a direct lateral approach with a minimum of temporal lobe elevation. Opening the animal's mouth will depress the coronoid process if this should interfere with the operator's view. On the right, the side of the counter-opening, there is no necessity for removal of the zygoma.

The denuded skull is trephined on both sides and the openings enlarged with rongeurs, wax being usually necessary to control diploic bleeding. The opening on the right becomes roughly oval in shape and averages about 3 by 3 cm. in a small dog—it can hardly be too large: on the left the bone is rongeured away, as far down as possible toward the cranial base so that the resultant opening has a more triangular form. The dura on the right is widely opened by an incision concentric with the bone defect: on the left, the side chosen for the approach, it should remain intact at this stage.

The special retractor is then introduced in the lower angle of the defect on the left, and as the dura is separated from the bone it is passed along the floor of the temporal fossa until the trigeminal line of dural attachment is encountered, where the membrane is strongly adherent. At this point the retractor is tilted and raised enough to stretch the dura, and with the hook-knife, which cuts from within outward an antero-posterior slit about 1½ cm. long is made, allowing the retractor to be pushed in beneath the exposed temporal lobe (Fig. 6). No further opening of the dura is advisable on this side, for the relatively intact membrane serves as an excellent protection for the overlying temporal lobe during its subsequent elevation. At this stage there is always a more or less abundant escape of cerebrospinal fluid.

From this time on an electric head-light is essential, for the gland lies deep and monocular vision is all that can be brought into play. Introducing the retractor still farther beneath the temporal lobe, the unmistakable landmarks leading to the hypophysis are made out (Fig. 4). Running from behind forward and downward the glistening third nerve is easily identified, and in front, the internal carotid artery passing upward to the base of the brain. The tip of the spatula is directed between them and the hypophysis brought into view. The gland appears as an elongated, rounded body, pinkish-white in color, which seems to dangle from the infundibulum, suspended by its stalk and directed backward toward the sella turcica, to which it seems but slightly adherent.

If the hypophysis is to be completely removed the closed blades of the forceps are first passed behind and beneath it, freeing it from its posterior vascular attachments. The stalk is then grasped, care being taken not to include the internal carotid artery, and the gland is drawn out. It may often be obtained in one piece (Fig. 18), but if it tears and a portion is left lying in the sella turcica this fragment can easily be lifted out with the spoon curette. Occasionally the tip of the infundibulum comes away with the gland (Fig. 19), but if con-

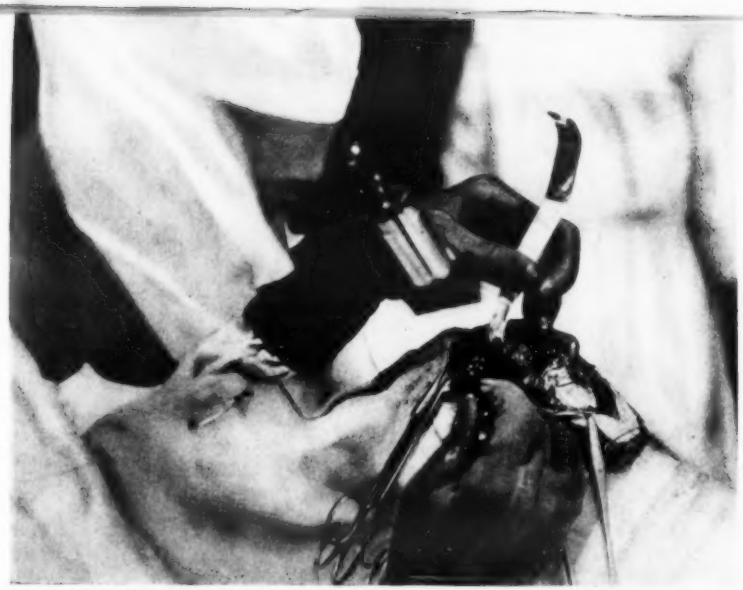

FIG. 6.—Near view of operative field, showing introduction of spatula with elevation of left hemisphere.

FIG. 8.—*Observation 80.* Mongrel puppy; 24 hours after partial anterior lobe removal.

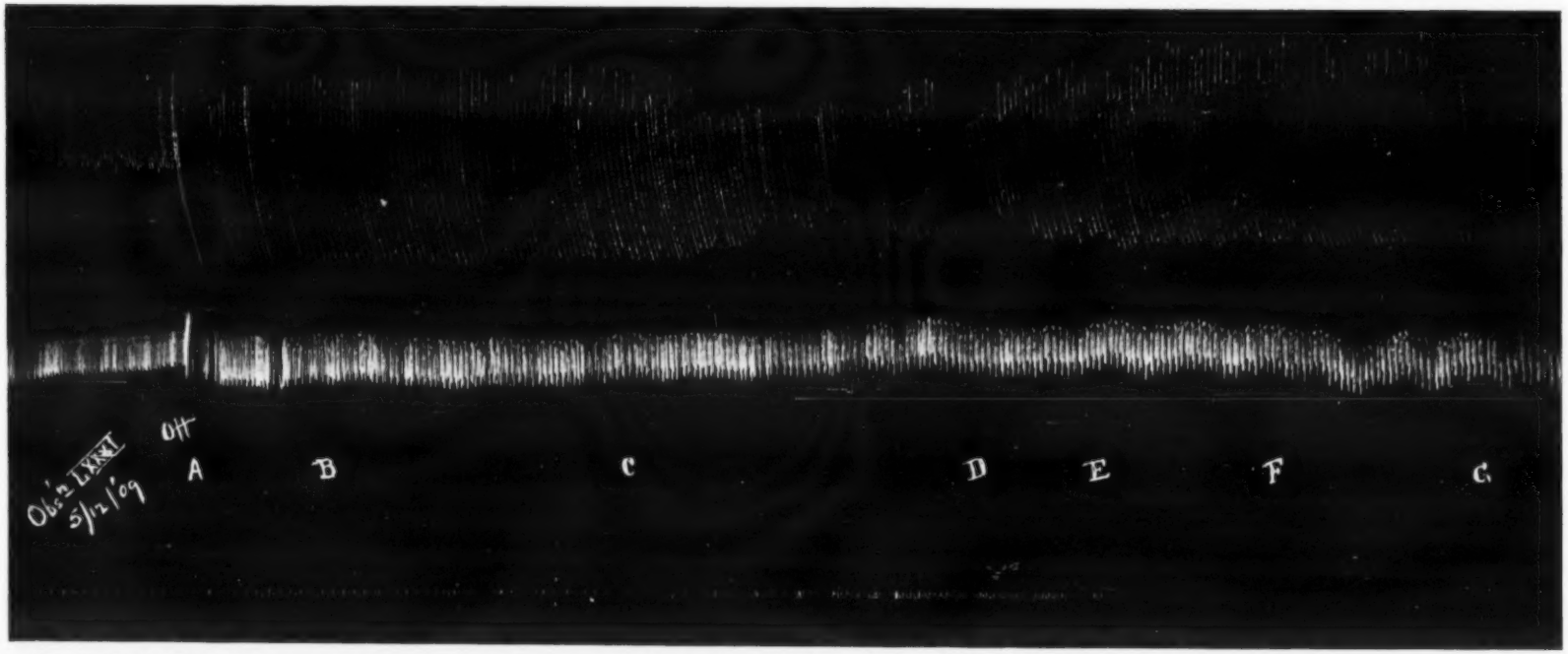


FIG. 7.—Record kept during course of partial hypophysectomy on *Observation 81* (cf. Fig. 38 and *Table VIII*), showing that the intracranial manipulation and removal of the gland produce no respiratory or vascular reactions. Following normal record, drum stopped at *A* during stages of operation preparatory to opening of dura. (*A-B*) introduction of elevator. (*B-C*) dura opened; escape of cerebro-spinal fluid; elevator introduced and temporal lobe elevated. (*C-D*) pars nervosa freed from posterior attachments and gland liberated. (*D-E*) stalk grasped and gland removed (presumably *in toto*); sponging. (*E-F*) third nerve intentionally manipulated and divided. (*F-G*) withdrawing from field; elevator removed, and brain released. (*G*) beginning closure.

ditions are less favorable the upper end of the stalk may remain in place with a minute fragment of pars anterior clinging to its anterior edge.

The bleeding caused by these procedures is moderate and can be controlled by the insertion of wisps of sterile cotton, which makes the best material for sponging. Needless to say, all manipulations must be made directly under the operator's eye: this is no place for a "blind" operation.

Of the possible complications, injury to the carotid is necessarily fatal; injury to a venous sinus, though controlled by packing, will prevent the satisfactory completion of the operation. Such accidents should be rare in experienced hands. In our earlier cases we occasionally so contused the third nerve as to cause permanent dilatation of the pupil, but of late this has rarely occurred. The same is true of injuries to the temporal lobe, which were occasioned in some of our early cases, leading to the peculiar rotary progression which characterizes a pyramidal tract lesion in the dog. The converging fibers of this tract lie very close to the surface of the temporal lobe at the most favorable point for elevation, and any cerebral laceration there is likely to produce motor symptoms, which might be easily misinterpreted.

When the field of operation appears dry after removal of the cotton packing the retractor is carefully withdrawn and the temporal lobe settles back in place, plastering the dura with its small incision against the skull. On the side of the counter-opening the dural flap is laid back but likewise need not be sutured. The divided muscles are reunited with fine silk sutures, care being taken to close all spaces where collections of blood might occur. The galea is brought together as a separate layer, and the skin closed with interrupted silk stitches. No drainage is used and the wound is left without a dressing, for bandages have been found to be unnecessary and they are annoying to the animal.

Since the operator should concentrate his attention steadily on the position of the retractor during the crucial part of the procedure, skilled assistants are, of course, a great advantage, and with their aid (Fig. 1) it is not unusual for the operation to be completed within an hour after the beginning of anæsthesia; nevertheless, with increased experience many of the later operations have been conducted (by Crowe or Goetsch) single-handed, with an anæsthetist.

3. *Effect of the Operation in Itself.*—In view of this extensive intracranial procedure, the question will naturally be raised: Are not the fatalities directly attributable to the operation itself rather than to the removal of the hypophysis? This was a personal criticism which carried much weight in the earlier stages of our work, when "neighborhood" injuries on the part of the nervous system were occasionally produced. Admitting it to be an elaborate, delicate and time-consuming performance, nevertheless our later series has been almost entirely exempt from operative or post-operative complications of any kind, whether from cerebral injuries or from hæmorrhage or infection.

One who is unfamiliar with intracranial procedures of this kind would be led to believe that the operation of itself would be tremendously disturbing in its effects. Many physiologists are under the impression that cerebral manipulations are invariably shock-producing affairs, and Cyon's description of the circulatory disturbances said to follow the mere mechanical stimulation of the pituitary body, which, therefore, was supposed to exercise some regulatory control over the cerebral blood supply, might make this result even more likely in the case of the operation under discussion. In all probability, were a bilateral opening not made, the necessary elevation of the temporal lobe would lead to a certain slowing of the pulse and rise in blood pressure—a physiological response on the part of the medulla due to compression alone. Such a response used to be observed during the act of exposing the Gasserian ganglion in man—a similarly conducted procedure, as has been pointed out, and one which necessitated temporal lobe elevation without the possibility of cerebral dislocation.

As an evidence, however, of the undisturbing nature of this hypophyseal operation and to show that no alterations in respiratory or vascular rhythm need occur during its progress, one of the hypophysectomies was conducted while a kymographic record was being taken (Fig. 7). Were further evidence needed that the operative manipulations of themselves cannot be responsible for the disturbances we are to describe, it should suffice to say (1) that they do not occur when the same manipulations are carried out and the gland crushed or fragmented but not removed—a performance which entails more loss of blood and more local trauma than a comparatively bloodless total extirpation; and (2) that 24 hours after all "partial" and most "totals" the majority of the animals are as lively and well as before (Figs. 8, 9, 10, 14, 15 and 23).

## V. Personal Operative Experiences.

### (a) total hypophysectomy.

Following the preliminary observations made in 1907 and 1908 by Reford and Cushing, we have made a more detailed study (1908-1909) of a much larger series of canine hypophysectomies conducted after the method described. Our primary object was not so much a further proof of the essentiality of the gland as it was (1) to attempt the tiding over of states of cachexia hypophyseopriva by feeding, injection or transplantation; (2) to observe the late consequences of partial removals, and (3) to study the effects upon the other ductless glands of hypophyseal lesions. However, in the course of these studies a certain number of total extirpations were made (21 in all) and as they were histologically proven to be total—a precaution neglected by Reford and Cushing—and as they bring out additional matters of interest, a tabulation of the cases may be given, to lead up to the more difficult and hitherto neglected study of the partially hypophysectomized animals suffering from grades of hypopituitarism. We have, furthermore, included in our series of 100 cases a number of the animals being studied at present (1909-1910) for other purposes by Dr. Emil Goetsch, making all told some 150 experiences, histologically corroborated, from which we may draw our conclusions.

As has already been stated, we soon learned that the opera-

tion was more difficult on old dogs—chosen at the outset owing to their larger cranium—and, unaware that age had any bearing on the final outcome, we began to select younger animals and finally puppies for the larger number of the operations. Some of the animals survived for so long a time before the onset of the expected symptoms of cachexia hypophyseopriva—some, indeed, supposedly (from an operative standpoint) subjected to a total removal failing to show any symptoms whatsoever—that for a time fresh doubts were aroused in our minds as to the actual essentiality of the gland.

As soon as we began to tabulate our results, however, on the basis of the microscopic studies, it was quickly appreciated that the cases fell into 2 groups, the life of the adults averaging 2 or 3 days, instead of 24 hours, as reported by Paulesco, whereas that of the puppies averaged 11 days, the longest duration after a confirmed total removal being 20 days. Viable anterior lobe fragments were found in every case of survival for a period of

FIG. 9.—*Observation 58;* mongrel puppy hound. Photograph taken the day after hypophysectomy. Note the animal licking his chops at sight of the proffered bone.

several weeks. It will be seen, however, that many of the animals, whose life depended on the retention of viable though minute fragments, possessed a greatly lowered resistance and often died from acute cachexia hypophyseopriva, even after long post-operative intervals, if called upon to withstand unusual conditions, such as infections or exposure or digestive disturbances.

The greater duration of life in the younger animals may possibly be due to their greater physiological elasticity, the other glands of internal secretion being able to assume, to a certain extent, the hypophyseal functions—a view receiving some support from the histological alterations observed in other organs, more particularly in the thyroid, and which we have interpreted as an hyperplasia. It is possible too that the pharyngeal "rest" of the gland which Haberfeld has described [26] as being fairly constant, may prove capable of a certain functional activity in young animals. But however we may attempt to explain the longer life of the hypophysectomized puppy, the clinical symptoms when they finally occur and the ultimate results of total removal of the gland in all of the 21 cases in our series and the 14 additional cases of Goetsch, have been the same, irrespective of age.

1. *Symptoms of Cachexia Hypophyseopriva (Apituitarism).*[27]

Though confused in many instances by complications attributable to surgical neighborhood injuries, certain of the manifestations of apituitarism nevertheless seem undoubtedly to have been observed during their experiments by Marienesco, Vassale, Biedl, Caselli, Pirrone, Paulesco, Livon, Reford and Cushing. After uncomplicated operations they are sufficiently characteristic, when once clearly recognized, to be thereafter unmistakable.

FIG. 10.—*Observation 94.* Mongrel collie, tugging at bone the day after a supposedly total hypophysectomy (subsequently proven partial) with cortical transplant.

As has been stated, the majority of the animals so promptly recover from the anæsthetic that they are soon on their feet and will lap water or milk in a short time: many of them, indeed,

[26] Haberfeld: Die Rachendachhypophyse, etc., *Beitr. z. path. Anat. u. z. allg. Path.*, 1910, XLVI, 133-232.

[27] In this section we are considering symptoms of so-called *cachexia hypophyseopriva* due to total loss of the gland leading to a state of anatomical *apituitarism*. We may, of course, meet with the same symptoms in suggestive and transient form, or even full-blown in case a persisting fragment of the gland has temporarily or permanently given out, producing transient or ultimate physiological apituitarism. Hence *apituitarism* and *hypopituitarism* overlap, but we have restricted the term *hypopituitarism* to the long-enduring states of glandular insufficiency not incompatible with the maintenance of life under favorable conditions. *Hyperpituitarism* is as yet a state which does not lend itself readily to

eagerly take solid food within 24 hours, in spite of the recent bilateral detachment of the more important masticatory muscles (Figs. 9, 10). Nevertheless, the adult animals, by the second or third day, though showing no change as yet in pulse, respiration or temperature, are, as a rule, noticeably less lively and responsive than those subjected merely to a partial removal. They are less interested in their surroundings, respond less readily to cajolery, are often irritable, and either return to their cages when given freedom or seek out and curl up in a quiet, warm corner. Certain changes in the urine, to be described, may be present.

A slight lowering of the body temperature is the usual inaugural symptom, but one of the first obvious signs is an unsteadiness of gait, with a certain stiffness of movement, particularly in the hind legs. This soon becomes exaggerated and the animal stands (Figs. 11, 12 and 26) or walks with a noticeable awkwardness, often showing a peculiar arching of

Fig. 11.—*Observation 36.* Adult fox terrier; a total removal 10 days after preceding heterogeneous transplant in bone marrow. Photograph taken 4 days after operation, showing typical attitude, with arching of back, etc., characteristic of onset of cachexia hypophyseopriva.

the back, suggesting at times, except for the incurved tail, the canine defæcation attitude. The body temperature continues to fall and before the end drops rapidly (6° to 8° C. in a few hours), until it may even approximate that of room temperature; particularly in the winter months the body may cool to an extraordinary degree—to 18° C. in one case, a loss of over 20° C.—in spite of external coverings. The blood pressure falls and the pulse becomes feeble, irregular and unusually slow. Respiration, becoming largely diaphragmatic, slows until it may register only 3 or 4 to the minute (Fig. 13). Occasionally tremors are observed, but more characteristic are coarse rhythmic, spasmodic twitches of the body musculature. These are often inaugurated by an involuntary act, such as that of respiration, or may be elicited by the slightest external stimulus. Spasmodic opening of the jaws, with frothing, is frequently seen. The normal deep and superficial reflexes are retained to the end and often are exaggerated.

Lethargy becomes pronounced and the animal, difficult to arouse, becomes indifferent to the comforts of bedding or to the soiling from evacuation. Euthanasia seems complete, and though still conscious enough to respond with a movement of apparent recognition to the voice, there seems to be complete

Fig. 12.—*Observation 60.* Fox terrier puppy, 14 days after total removal (cf. Fig. 21). Symptoms of cachexia hypophyseopriva of 3 days' duration and more advanced than shown in Fig. 11. Photograph a few hours before death. Temperature 22° C. Respiration 6 to the minute (cf. Fig. 13).

anæsthesia to a painful stimulus, such as a pin-prick, or even to the taking of a direct blood pressure record from the femoral artery (Figs. 13 and 16). Finally a deep coma ensues and the transition from this state to death, occurring without a struggle, is so imperceptible that it is sometimes difficult to tell just when the end has come.

In commenting on certain resemblances between cold-blooded animals and the dogs in this state of subnormal temperature, Dr. Goetsch has called our attention to the fact that the heart, like the batrachian organ, will continue beating long after its removal from the body, and will contract on mechanical stimulus for an hour or more; also to the fact that the blood, after death, has an unusually bright red color, despite the unaerated condition one would expect in view of the marked slowing of respiration.

experimental study, but our results in this direction will be subsequently recorded.

These terms, representing states of *dyspituitarism*, as employed here have reference to the entire pituitary body, with full appreciation of the fact that the experimental states we are portraying are associated with disturbances of the pars anterior alone. When we possess a more complete knowledge of the gland and its various functions it will doubtless be necessary to construct a terminology which will indicate conditions of over or underactivity of each of the subdivisions of the gland.

FIG. 13.—Fragment of record taken from femoral near terminal stage of coma in *Observation 69* (total hypophysectomy in a puppy); showing respiration 2-3 to the minute; pulse 40 and blood pressure 14 mm. Hg. Temperature at this time 22° C.

FIG. 14.—*Observation 64.* Puppy (4 months of age), playful and bright-eyed and apparently without symptoms 7 days after *total* hypophysectomy.

FIG. 15.—*Observation 89;* collie puppy. Photograph taken day after total removal, showing apparently normal animal eagerly dragging at a proffered bone.

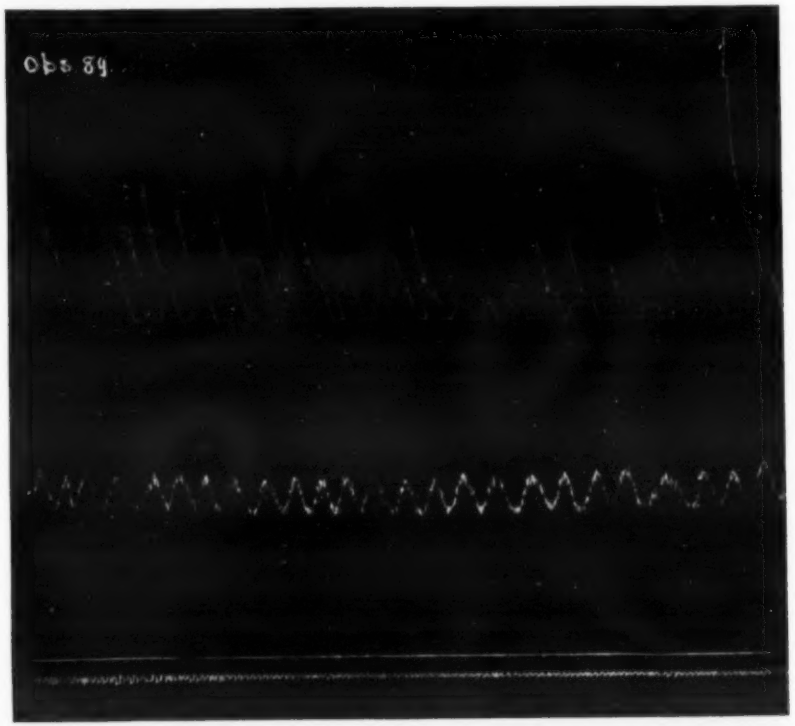


FIG. 16.—*Observation 89.* Record made just before death. Temperature 33.2° C.; respiration 10; blood pressure 23 mm. Hg., and pulse 150 (unusually rapid for this stage).

This entire transition from an apparent state of well-being may take place, particularly in adults, in the course of a few hours, though more often premonitory symptoms may set in a day or so before death. The more gradual onset is usual in the case of the younger animals, and, as will be shown later on, animals, after a nearly total removal, may show transitory symptoms which subside spontaneously or which may be interrupted by glandular transplantations or by injections of hypophyseal extract.

In order to emphasize the much longer duration of life in the young animals we have separated them from the adults in the tables to be given. This, however, remains practically the only distinguishing feature of the 2 groups (compare *Table II* and *Table III*).

2. *Results of Total Hypophysectomy in the Adult Canine* (*Table II*).—There prove to have been 13 cases; in all these the symptoms were allowed to run their course uninfluenced by transplants or glandular injections. As heretofore stated, the operation on old dogs, owing to the adherent and friable dura, is more difficult than on the young, and as most of them were performed early in our series, complications were more common. However, the results were controlled, as the case numbers indicate, by some additional observations on adults after we had become more expert.

In *Observations 6, 22, 44, 51* and *53* there were certain confusions from hæmorrhage, necessitating a piecemeal removal with an occasional temporal lobe and oculomotor injury: the remaining 9 operations were conducted without complication. Only 2 of the animals (*Observations 22* and *53*) succumbed in the first 24 hours, as did the majority (58 per cent) of Paulesco's 22 canine totals, which included young animals as well. On the other hand, only 2 of Paulesco's series lived over 36 hours, whereas all but 2 of ours survived this period, the longest duration being 5 days and the average nearly 60 hours.

The characteristic symptoms of apituitarism occurred in all cases. A marked diminution of the urinary output, even to anuria, was common, and a transient glycosuria was occasionally observed (*Observations 57* and *67*).[28] Thus in *Observation 57* the urine reduced Fehling's solution for 2 days after the operation, but failed to do so on the third day, and the urine in the bladder at autopsy 24 hours later had no reducing properties. In only 1 case (*Observation 44*) was there a wound infection, and this a superficial one.

Obvious histological alterations in the other ductless glands were first observed in the animals of this series, an enlargement with acute hyperplasia of the thyroid being the most noticeable change.

A typical protocol follows:

OBSERVATION 28 (*Table II*). An old, but apparently healthy male fox-terrier.

*December 4, 1908* (2 p. m.). An uncomplicated operation by the usual method. Gland removed in one piece apparently intact. Prompt recovery from the anæsthetic.

*December 5* (9 a. m.). Has entirely recovered from the effects of the operation. Has taken milk and water. Movements deliberate but otherwise normal. Left pupil dilated, showing operative contusion of third nerve, but no tendency to rotary progression due to temporal lobe and pyramidal tract injury: no arching of the back. Takes an interest in his surroundings and in other animals. Rectal temperature 38.7° C.; pulse 168; respiration 16.

(3 p. m.—24 hours after operation.) Much less active than in the morning. Lies curled up in a corner of the cage; is difficult to arouse. Will not stand or walk; tendency to arching of the back; refuses food and water. Rectal temperature 36° C.; pulse 160; urine for 24 hours 130 cc., no sugar.

(6 p. m.) Condition about the same as at last note. Rectal temperature has dropped to 35.2° C.; pulse 152.

*December 6* (9 a. m.) Comatose; cannot be aroused. Reflexes present but sluggish. Body feels cold. Rectal temperature 26° C.; femoral pulse barely palpable—48 to minute, very irregular; respiration 10 to minute. No urine secreted for the past 24 hours; frequent watery movements of bowels and an increased flow of saliva.

During the morning the pulse gradually became weaker and more irregular; the respiration grew more infrequent and apparently ceased about 2 p. m.

*Autopsy:* Immediately after death. No hypophyseal tissue is evident on gross examination, and subsequent study of a series of microscopic sections through the base of the brain shows the removal of the pars anterior and pars nervosa to have been complete. The tip of the infundibulum is closed by a small organizing blood-clot, above which is a fragment of pars intermedia in a condition of evident hyperplasia.

The thoracic and abdominal organs are macroscopically normal. The same is true of the ductless glands. The thyroid alone was examined microscopically and appeared normal (at this time we were not making complete histologic studies of these structures).

3. *Results of Total Hypophysectomy in Puppies* (*Table III*).—In our personal (1908-1909) series no attempt was made to influence the course of the symptoms of glandular transplantation or injection in 8 of the 15 puppy extirpations histologically proven to be total. These 8 are grouped with 11 of the "proven" cases from the 1909-1910 series of Dr. Goetsch, which though hypophysectomized for other purposes are valuable in this connection also. Many of the animals were born and raised in the laboratory, so that their exact age was known, but they were all under a year, as indicated by the teeth.

As stated, the approach to the gland is easier in these younger animals, in spite of their relatively smaller size, but at the same time one is more likely to leave a small fragment of the upper edge of the anterior lobe than is the case with attempted totals in the adult. Hence, in view of their surprisingly long survival, it became necessary to serially scrutinize all sections from the infundibular block for the presence of even a minute viable fragment embedded in the strata of scar tissue. Not uncommonly such a fragment may be found (Figs. 36 and 42), although at operation the removal has seemed complete and although gross post mortem appearances also indicate totality of removal.

These anterior lobe fragments, which are unmistakable, owing to their cellular arrangement and the presence of acid-

[28] More careful attention has been given to the alteration in the urine in our 1909-1910 series, and Dr. Goetsch has found that a transient early glycosuria is nearly always demonstrable in all totals.

ophiles, adjoin the pars intermedia (Herring) cells which are necessarily left adherent to the infundibulum. The pars intermedia, however, seems to play no part in the question of duration of life, as will be seen when considering anterior lobe removals with preservation of the posterior lobe and investing pars intermedia.

The shortest duration of life occurred in *Observation 59*, a puppy 3 months of age, raised in the laboratory. The animal never entirely recovered from the effects of the operation, but remained inactive, and succumbed on the third day, with the usual symptoms—a slow, irregular pulse, low blood pressure, subnormal temperature (29° C.) and coma. In our series, the longest survival (*Observation 58*) was 20 days, and 2 puppies in the 1909-1910 series (Goetsch) lived 22 days. The average duration was something over 11 days.

The young animals recover promptly from the anæsthetic, and on the following day, as a rule, they are as lively and playful as before the operation. During the succeeding days many of the longer-lived animals show a noticeable gain in weight and seem normal in every way (Figs. 14 and 15) until the abrupt onset of symptoms of cachexia hypophyseopriva. This state is commonly inaugurated by a premonitory subnormal temperature, which may precede the other manifestations for a few days. Then follow inactivity and unsteadiness of gait, which usually foretell an exitus within 24 hours.

A typical protocol follows:

OBSERVATION 89. Collie puppy; age 6 months; weight 12 pounds.

*May 28, 1909.* Hypophysectomy without operative complications; apparently a total removal.

*May 29.* Bright and playful. Eats heartily (cf. Fig. 15). Temperature 38.6° C.; pulse 180; urine 500 cc., no sugar.

*May 30.* Apparently normal in every way. Temperature 38.6° C.; pulse 136; urine 280 cc.

*May 31.* Continues free from all post-operative disturbances. Temperature 38.6° C.; pulse 146; urine 280 cc.

*June 1.* Regularly empties his food pan, but nevertheless has lost one quarter of a pound in weight. Temperature 38.5° C.; pulse 100; urine 120 cc.

*June 3.* Continues to be lively and responsive. Temperature 38.3° C.; pulse 80, regular; urine 130 cc.

*June 4* (8 a. m.). Sudden onset of symptoms of hypophyseopriva. Refuses food. Has lost all tendency to playfulness; lies sleeping in a corner of the cage; is difficult to arouse, but will walk slowly around the room when placed on the floor. Has marked arching of the back. Temperature 36° C.; pulse 92, barely palpable.

(2 p. m.) Perfectly comatose; lying at full length. Respiration slow and deep, largely diaphragmatic, 10 to minute. Temperature 33.2° C.; pulse 100, regular but difficult to palpate.

Without an anæsthetic being necessary a canula was placed in the right femoral artery and a record made of the blood pressure at 46 mm. Hg., with the pulse 150 (?) and respiration 10 (Fig. 16). Death occurred at 6 p. m. The animal's weight was 11½ pounds.

An immediate *autopsy:* No remains of the hypophysis were evident in gross and the serial sections failed to show any remaining anterior or posterior lobe tissue. A few pars intermedia cells undergoing hyperplasia remained attached to the infundibular stalk.

The abdominal and thoracic organs were normal, with the exception of what appeared to be an extreme fatty degeneration of the liver. The ductless glands showed: Thyroid, slight hyperplasia; adrenal, vacuolization of lower layer or zona reticularis clearly demarcating cortex from the medulla, which showed definite hyperplasia; thymus, though large, showed no recognizable change; pancreatic islets unusually large and distinct, with a peculiar arrangement of cells; ovaries, no recognizable change.

This protocol is that of one of the shorter-lived animals in this series, but the interval of well-being before the abrupt onset of the terminal symptoms is equally striking in the cases of those surviving for a period of 3 weeks.

A post-operative polyuria has been frequently observed in the puppies, contrasting with the opposite condition seen in the adults. Even in the 3-day case (*Observation 59*) 300 cc. was voided during the 24 hours after the operation, whereas 150 to 200 cc. is a fairly normal average. In each of the 7 remaining animals of the 1908-1909 series there was a polyuria varying from 500 to 1500 cc., which in some instances persisted for many days until the onset of the terminal symptoms, shown by a drop in body temperature, when the amount rapidly diminished, in some cases anuria preceding death. No reducing substance was observed in our cases, doubtless, in view of Dr. Goetsch's results in the 1909-1910 series, due to our failure to look for it during the first few hours after operation.

An indication of the reactionless healing is shown by the absence of post-operative pyrexia (cf. tables) in these animals: in only 1 instance (*Observation 65*) was there a day's febrile response of 1.4 degrees. The terminal drop in body temperature occurred in many cases during the last day of life, as in *Observations 58* and *70;* but this is not invariable as shown by *Observation 60*, in which the temperature reached its lowest registration at 22° C. after a gradual fall extending over ten days (Figs. 12 and 21). Efforts were naturally made in many cases to prevent this excessive lowering of body temperature, and though it could be raised many degrees—in some cases even to normal—by artificial measures, excessive panting would be brought on and the animals invariably seemed the worse for the attempt. It was observed, however, that the muscular tremors and spasmodic movements lessened with the rise in temperature.

4. *Hypophysectomy in the Cat by the Buccal Route.*—Although it is with the results of the canine operation that we are chiefly concerned, in view of Gemelli's contradictory experiences to which we have referred it may not be out of place to record certain observations made by one of us (Homans) in an effort to substantiate his findings. Owing to its wide and shallow mouth, the cat is the only available species in which even approximately accurate results may be expected by the buccal method of approach. A brief description of the feline operation follows:

Anæsthesia is administered with the patient on its back. A pad is placed under the neck so that the roof of the mouth slopes downward and forward: the jaws are held widely open and the tongue drawn out. The mouth is carefully cleansed with 50% alcohol. The soft palate is divided in the median line from the edge of the hard palate in front nearly to its posterior margin. A stitch is then taken on each side of this incision and the ends of the thread drawn out, holding the edges of the wound apart. Through this

opening the roof of the pharynx is exposed, cleansed and incised, the center of the 1½ cm. incision being at a point midway between the easily identified pterygoid processes. The edges of the incision are scraped back, exposing a median bony ridge, in which is a small opening for the passage of a blood vessel. The bone should be penetrated with a trephine, drill or guage, just posterior to this point, but the exact position of the primary opening is not of vital importance, since the hypophyseal pocket of dura is easily indentified and the opening can be enlarged backward or forward as needed. When finished (5 to 6 mm. in length by 4 or 5 in width) it should expose at least the anterior two-thirds of the gland and should extend for perhaps 2 mm. in front of it. The dural pocket is then incised and pushed to either side. A fine curette is passed into the back of the sella turcica, the posterior attachments of the gland divided, and the structure tipped forward as far as possible without rupture. Fine forceps are then passed in through the opening, one blade on either side of the stalk, and the gland drawn out. It rarely comes away intact, but the procedure causes so little bleeding that some at least of the remaining fragments can generally be picked out with the forceps or curette. The opening is then closed with bone-wax, the mucous membrane laid over it and the soft palate sutured.

Before the operation urotropin (gr. xxx) is given by a stomach-tube, and the comparative freedom from infection in our cases may be attributed in great measure to this precautionary measure.

Though eventual complete disintegration of the gland may generally be inferred when the infundibular opening in the floor of the third ventricle is seen with no hypophyseal tissue about it, there is always a possibility that fragments of anterior lobe may remain in the sella turcica detached from their normal position. Unless such a large opening is made as to greatly increase the danger of hæmorrhage or infection this possibility remains and constitutes the chief objection to the buccal operation.

In the 8 animals subjected to this operation the anterior lobe extirpation proved to have been total in only 2: the others on histologic examination showed remaining fragments of the gland, which in some cases were doubtless viable. All but 1 of the animals, nevertheless, succumbed in the course of a few days. In some of them the symptoms of cachexia hypophyscopriva were masked by those of infection, meningitis or hæmorrhage; but in the few cases free from surgical complications the symptoms were typical. Polyuria was constantly observed, glycosuria occasionally; and the low body temperature and motor disturbances preceding coma and death were in all respects identical with those of canine apituitarism.

A protocol follows:

Observation 84. Male kitten; weight 2 pounds.

*May 19, 1909.* Buccal operation without complication. Extirpation fragmented but apparently complete and showing infundibular opening. Urotropin by tube. Prompt recovery from ether.

*May 20.* Seems well and lively: takes nourishment.

*May 21.* Palate wound clean. Laps milk with urotropin. More quiet, but no meningeal symptoms. Temperature 38.4° C.

*May 22.* Onset of usual symptoms. Unsteadiness, muscular tremor, arched back, etc. Temperature 28.3° C.; deep, slow, diaphragmatic respiration. Constant urination, involuntary (?). With artificial heat temperature raised from 28° C. to 35.5° C. by noon, and to 37.7° C. by 5 p. m.

*May 23.* Condition about as yesterday, but very lethargic.

*May 24.* Died during night.

*Autopsy:* Wounds in palate and at base of skull clean. No meningitis or hæmorrhage. No gross evidence of retained hypophyseal fragments about infundibular stalk. Histological examination nevertheless shows a degenerated fragment of anterior lobe infiltrated with leucocytes and fibroblasts. Serial sections through entire infundibular region confirm total absence of viable anterior lobe cells. Many hyaline globules passing from remaining hyperplastic fragment of pars intermedia toward infundibular cavity.

Thoracic and abdominal organs macroscopically and microscopically normal. Ductless glands: no recognizable change; possible hyperplasia of adrenal medulla.

One animal which survived for a considerable time without showing symptoms, was sacrificed after 34 days, and, as anticipated, a fragment of anterior lobe of considerable size, which was viable, was found to have been overlooked at the operation.

Without going further into the details of these 8 cases, even this small experience with the buccal feline operation showed us (1) the frequency of complication (hæmorrhage and infection) by this method (3 cases); (2) the rarity with which at the operation totality of removal could be assured; (3) the fact that proven total removals in uncomplicated cases led to fatality in the expected interval with the usual symptoms of cachexia (2 cases), and (4) that survivals for a long period indicated incompleteness of removal.

5. *Criterion of "Total" Removal.*—To avoid any misunderstanding it seems advisable to indicate clearly just what we have meant to convey in the foregoing sections by "histologically proven total hypophysectomy." For control a median longitudinal section of the normal canine gland is shown in Fig. 17. Fig. 18 likewise shows a median section through the intact gland after extirpation in *Observation 63*, and Fig. 19 the base of the brain from the same animal as removed after death 4 days later. By no means does the gland always come away as intact as the one here shown, though probably this has been accomplished in 50 per cent of the observations planned to be total removals. The infundibulum, as can be seen, is open, and fragments of pars intermedia underlie the nervous tissue still constituting the floor of the third ventricle. It is obvious (Fig. 17) that in grasping the stalk even of the dangling gland [29] a fragment of anterior lobe could easily be crushed off and left in place (at the point B of Fig. 17) and Figs. 36 and 42 show how minute a fragment may serve the physiological needs. These anterior lobe fragments in the "partial removals" usually give evidence of hyperplasia (Fig. 36), and the same is true (Fig. 27) of the fragments of pars intermedia which inevitably remain even in the "total removals."

Whatever the function of the pars intermedia may be, it is of less vital moment to the individual than is the anterior lobe, as we shall see when considering the effects of partial removals. Further illustrations of the infundibular condition in other "totals" (*Observations 52* and *60*) are shown in Figs. 20 and 21, and a surgically supposed "total," which histologically was found incomplete, is given in Fig. 22.

The *conclusion* may be drawn from these experiences, in agreement with Paulesco, that the total removal of the hypophysis leads to a train of symptoms which characterizes no other known clinical condition and which, therefore, may safely

[29] The sections (Fig. 17) naturally show the gland in an abnormal position flattened against the base of the brain. The structure during life hangs away, a postural peculiarity which is accentuated by the surgical dislocation upwards of the cerebrum.

be ascribed to the loss of the gland, particularly in view of the fact that precisely the same operative manipulations which stop short of actual removal of the gland lead to none of these symptoms whatsoever.

FIG. 17.—Normal control. Median section through base of brain and intact gland. For comparison with Figs. 18 and 19. *A*, third ventricle; *B*, junction of pars anterior and intermedia; *C*, cleft; *D*, pars nervosa; *E*, anterior lobe; *F*, optic chiasm.

FIG. 18.—Median section of the entire gland of *Observation 63* (*Table II*), as removed at operation (cf. Figs. 17 and 19).

This does not mean, of course, that animals with a retained fragment of anterior lobe will necessarily remain entirely free from all manifestation of hypophyseopriva symptoms, for although we have evidence that an exceedingly small fragment may, under favorable circumstances, support life, nevertheless animals with a "nearly total" removal may succumb as promptly as the totals, provided the removal is physiologically complete, the functional activity of the fragment being interfered with; and not infrequently, as we shall see, some of the nearly total removals show transient symptoms from which they may recover, which is never the case with anatomically total removals. We have found furthermore that the animals

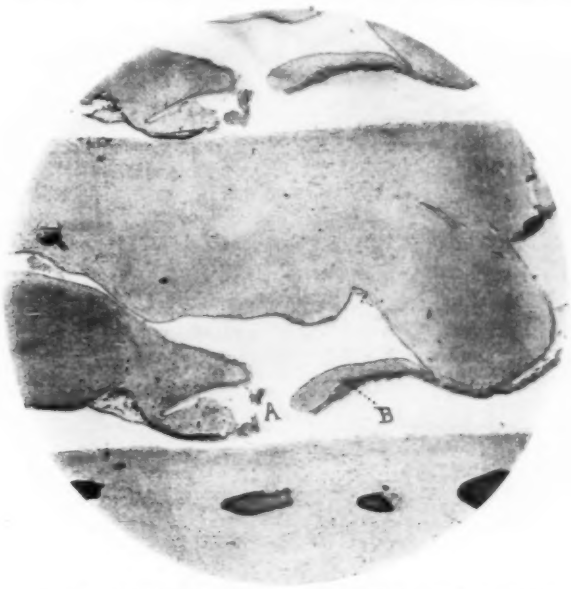


FIG. 19.—Median section through base of brain in *Observation 63* (*Table II*) 4 days after total hypophysectomy (cf. Figs. 17 and 18). *A*, open third ventricle; *B*, residual fragment of pars intermedia.

FIG. 20.—Median section of base of brain of *Observation 52* (*Table II*) 36 hours after adult hypophysectomy, showing slight extent of contusion.

with nearly total removals can be permanently tided over the period of threatened symptoms by glandular therapy, and it is possible that with improved methods of administration the same may be accomplished for the totals, but as yet, though we have been able to prolong life, we have not succeeded in the permanent saving of any of the "totals."

6. *Total Hypophysectomies Modified by Transplantations and Injections.*—It will have been noted that our experiences with something over 125 operations have given us comparatively few uncomplicated "totals," namely, the 15 questionable ones in the 1907-1908 series, the 21 adults and puppies of the 1908-1909 series (*Tables II* and *III*) and the 14 puppies of Dr. Goetsch's 1909-1910 series. This, however, does not include all of the "proven total" extirpations of our personal series, for the progress of the symptoms has been modified in a number of instances by transplantations or by injections in such a way as to make it inadvisable to include them in the

FIG. 21.—Median section 15 days after total hypophysectomy in *Observation 60* (*Table III*). Showing average amount of remaining pars intermedia, open ventricle and absence of contusion.

foregoing table, the primary object of which is to accentuate the duration of life in states of *unmodified* post-operative apituitarism.

The results of our 23 *transplantation experiments* have already been published.[39] The grafts were placed either under the rectus muscle, in the bone-marrow, according to the method of Kocher, or in the right cerebral subcortex exposed during the operation. We were much more favorably impressed by the latter method as being especially convenient for immediate isotransplantation of the removed gland. In 3 of these cases (*Observations 4, 13* and *99*) the hypophysectomy was subsequently proven to be total. In *Observation 13* the animal died in 48 hours after the usual symptoms, and the engrafted tissue was found completely necrotic. In *Observation 99* (protocol given, *loc. cit.*) an adult animal surviving the usual fatal period was sacrificed at the end of 18 days, no symptoms whatsoever, beyond a transient glycosuria, having been observed; a peripheral zone of normally staining, viable anterior lobe cells surrounded the necrotic center of the graft, and colloid bodies were abundant in the adjoining cerebral tissue. In *Observation 4*, on the other hand, transient symptoms of cachexia hypophyseopriva appeared on the second day, but subsided, and the animal was sacrificed on the 15th day, at which time the graft showed a peripheral zone of normal appearing anterior lobe cells with hyaline bodies, presumably from the pars intermedia, in the surrounding brain.

At the time of these experiments we were greatly surprised to find so narrow a peripheral zone of still viable cells, for we did not then realize how minute a fragment of anterior lobe suffices to maintain life under favorable circumstances. Had

FIG. 22.—Supposed total hypophysectomy after 48 hours. Showing adherent blood-clot in which remains a tag of pars anterior.

this been appreciated we might have looked more favorably on the condition of the bone-marrow heterotransplants engrafted before the hypophysectomy, for we regarded them at the time as so far degenerated as probably to be functionless. The condition of the immediate autotransplants of the surgically extirpated glands was better, due doubtless to the principle emphasized by W. S. Halsted as the result of his parathyroid experiences, namely, that an existing physiological deficit is an essential factor to a successful "take." In the few cases in which the homogeneous gland was implanted a day or two after the hypophysectomy its beneficial effects in tiding over symptoms of cachexia and thus prolonging life was more apparent than when it had been implanted a few days before the operation.

The crucial test of removing the graft itself from one of the

[39] Effects of hypophyseal transplantation following total hypophysectomy in the canine. *Quart. J. Exp. Physiol.*, 1909, II, No. 4, 389.

animals with a primary total removal, or of completing a partial hypophysectomy by a second operation was attempted several times. We were frustrated in both of these tests, on the one hand because in several of the animals from which the graft had been removed no symptoms occurred and we subsequently found a minute anterior lobe fragment at the base, and on the other hand because in a second-stage approach to the sella turcica it is almost impossible to secure a clear and bloodless view.

This portion of the work needs careful repetition and amplification, but from the 7 observations with grafts in cases of proven total removal we feel justified in the conclusion that there was a distinct prolongation of life through these means. We shall see later on that implantation of homogeneous grafts, when symptoms of cachexia hypophyseopriva arise after almost total removals, will often serve to tide the animals over this critical period.

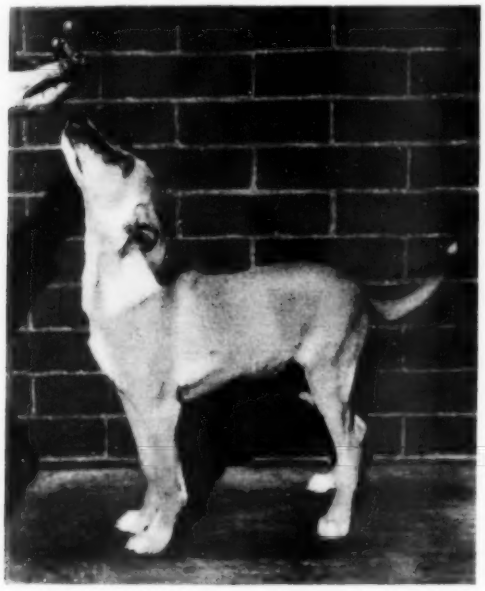

FIG. 23.—*Observation 85.* Mongrel puppy 24 hours after posterior lobe removal. No symptoms. Eagerly expecting proffered bone.

Our *injection experiments* likewise were made upon a number of proven totals with results which we withhold for later comment.

### (B) PARTIAL HYPOPHYSECTOMY.

1. *Effects of Posterior Lobe Removal.*—In view of the fatal consequences of removing the entire gland, the next step naturally was to determine which of the 2 surgically divisible lobes is the more essential to the maintenance of physiological equilibrium, so strikingly upset by the loss of the structure as a whole. In consequence of its well recognized physiological properties, akin in many respects to those possessed by the adrenal medulla, it would have been a natural supposition that the posterior lobe, with its epithelial investment (*pars intermedia*—Herring) would prove to be the essential fragment.

In the dog the spherical posterior lobe, owing to the well preserved cleft may be easily dislodged from its position in the cup-shaped pars anterior with little or no disturbance of this anterior portion of the gland, the only attachment of any importance being the few columns of anterior lobe cells which mark the transition between pars anterior and pars intermedia (Fig. 17).

Paulesco made 5 experiments of this nature and concluded that this portion of the gland is not essential to life. One of his animals died with convulsions 2 years after the operation; the other 4 lived from 13 days to 8 months, succumbing to an epidemic of broncho-pneumonia in his kennels. No symptoms were observed, with the exception of terminal convulsions in the one animal.

As will be seen by the accompanying table (*Table IV*) we have had in our 1908-1909 series 3 uncomplicated observations of this character, and these have been supplemented by several others in the 1909-1910 series.

In our series there were also many other cases in which, purposefully or accidentally, not only the posterior lobe, but some of the pars anterior was removed as well: these will be considered under a separate grouping (*Table VIII*).

Of our 3 unmodified (by transplantation) and uncompli-

FIG. 24.—*Observation 86.* Posterior lobe removal; normal condition 24 hours after operation.

cated cases, one (*Observation 25*) was sacrificed after 6 months. The animal during this period had a number of peculiar convulsive attacks with maniacal excitement. A more or less persistent erotomania also characterized the post-operative history; and the same has been true of one of the animals in Dr. Goetsch's 1909-1910 series—a condition of sexual activity, the reverse of that seen after loss or diminution of anterior lobe function.

Of the other 2 posterior lobe removals, *Observation 86* (Fig. 24), a puppy, seemed in normal condition when sacrificed on the 50th day. The blood supply of the anterior lobe must have been affected, as in the stalk separations (*Table VI*), for this part of the gland was almost completely degenerated, there being only one small focus of normal appearing cells. The animal had become fat, showing a gain of 3 pounds in weight. *Observation 85* (Fig. 23) died on the 23d day without any

of the symptoms of cachexia hypophyseopriva. The anterior lobe was in very good condition and all other organs were normal, except the liver, which was extensively degenerated and showed only scattered areas with fairly normal cells.

An illustrative protocol follows:

OBSERVATION 25 (*Table IV*). *Extirpation of posterior lobe; convulsions; erotomania; sacrificed after 6 months.*

*December 4, 1908.* Adult male bull terrier; weight 18¾ pounds. *Operation:* Total uncomplicated posterior lobe removal; no operative complications.

*December 5.* Bright and playful; eats heartily. Temperature 38° C.; pulse 160; urine 200 cc., no sugar; weight 18½ pounds.

*December 6.* Animal lively; appetite good. Temperature 38.6° C.; pulse 140; urine 300 cc., no sugar.

*December 19.* Wound has healed *per primam*. Seems normal in every way. Temperature 38.8° C.; pulse 140; urine 400 cc., no sugar.

*January 17.* Weight 20 pounds; temperature 38.6° C.; pulse 120; urine 320 cc., no sugar.

*February 8.* Continues apparently normal in all respects; allowed to run in paddock. Temperature 38.2° C.; pulse 90; urine 250 cc., no sugar; weight 20 pounds.

*March 22.* Since previous note animal has been in paddock, apparently in perfect health, though noticeably erotic. To-day he suddenly became very much excited; blindly running into the walls. Repeated severe convulsive seizures followed, with marked salivation. Was placed in a warm room and given ⅛ gr. of morphia.

*March 23.* Has entirely recovered. Three days later (March 26) again turned in the yard, though a nuisance owing to erotic tendencies.

*March 29.* Temperature 38.2° C.; pulse 96, irregular; urine 420 cc.; weight 18¾ pounds.

*April 14.* Appetite good. Temperature 38.6° C.; pulse 60, very irregular; urine 360 cc., no sugar. Erotomania persists.

*May 10.* Second series of convulsions similar to those of March 22; recovery within a few days. Temperature 37° C.; pulse 69, very irregular; no sugar in urine.

*May 30.* Temperature 38.4° C.; pulse 72; urine 280 cc.; weight 19½ pounds. Sacrificed under anæsthesia.

*Autopsy:* Body well-nourished; panniculus abundant. Brain and meninges appear normal on gross examination. Pars anterior intact, and though flattened is normal in appearance. Thyroids are slightly larger than normal and quite firm. Abdominal and thoracic organs appear normal.

*Microscopical Examination:* The portion removed at operation consists of the pars nervosa with its epithelial investment. The remaining anterior lobe is normal in appearance. There is a compensatory (?) hyperplasia of the remaining fragment of the pars intermedia and an unusually large number of colloid bodies are present in the brain tissue adjacent to the ventricle. Liver shows evidences of fatty degeneration (?). *Ductless Glands:* Adrenal, normal. Pancreatic islets, normal, though cells are possibly somewhat enlarged. Testis, tubules normal with active spermatogenesis; no change observable in interstitial cells.

In reviewing these few cases it is apparent that subnormal temperatures and other manifestations of cachexia hypophyseopriva have not been observed, and whether the maniacal and convulsive attacks and the erotomania can be safely looked upon as characteristic of posterior lobe removal will need further investigation. Certainly no symptoms of this kind have occurred among the large number of cases of posterior, combined with partial anterior lobe removal.

We have not observed any lowering of blood pressure or diminution in the urinary output—symptoms which might be expected in view of the known action of extracts of this part of the gland. One must bear in mind that fragments of pars intermedia which evidently undergo hyperplasia (cf. Fig. 27) are necessarily left behind no matter how clean-cut the operation may be, and an abundance of hyaline is to be found in the channeled spaces leading from these fragments to the infundibular cavity. In this respect the posterior lobe removals are necessarily less conclusive than those of the anterior lobe, but the following will show that the posterior lobe, even in its entirety, will not suffice to maintain life.

2. *Effects of Removal of the Anterior Lobe Alone.*—Dislocation and removal of the posterior lobe without accompanying damage to the pars anterior, though less easily accomplished than removal of the entire gland, nevertheless is a comparatively simple operation. Much more delicate and difficult, however, is the reverse procedure, namely, total removal of the pars anterior, leaving the posterior lobe in place, still attached to the infundibulum and with its circulation intact.

In 6 of our 9 attempts we failed in our object, as shown by subsequent histological studies. These animals all survived for periods of a number of days to 6 months, and histological studies showed viable microscopic anterior lobe fragments in each instance. They consequently have been transferred from this group to *Table VIII*.

In 3 instances (*Table V*) the extirpation was proven total, with a clinical picture identical with that following a total hypophysectomy.

A typical protocol follows:

OBSERVATION 7. *Microscopically proven total removal of anterior lobe with intact posterior lobe in place. Death in 68 hours from cachexia hypophyscopriva.*

Adult fox-terrier.

*October 8, 1908. Operation:* No complications aside from the usual bleeding of an adult craniotomy. Excellent view of gland, which was carefully manipulated until the two lobes were dangling separately. Cup-shaped anterior fragment removed apparently intact, leaving posterior lobe in place. Prompt recovery from anæsthetic. Animal walked downstairs to kennel 2 hours later.

*October 9.* No symptoms other than slight dilatation of left pupil. Takes water and milk eagerly. Active and shows no disturbance of gait. Temperature 39.2° C.; pulse 140; urine 420 cc., no sugar.

*October 10.* Wound in perfect condition. Animal inactive, dull and unreponsive. Refuses solid food. Polyuria (amount not measured; no sugar) and polydipsia. Temperature 37.2° C.; pulse 116.

*October 11.* Lethargic in early morning and refuses food but drinks freely. Subnormal temperature (32° C.); pulse feeble and irregular (60); respiration slow and deep, each inspiration accompanied by a spasmodic contraction of the diaphragm and abdominal muscles. Animal in deep coma by noon and death occurred suddenly at 2 p. m., with copious watery evacuation of the bowels; no convulsive seizures.

*Autopsy:* The posterior lobe was found in place; blood supply and stalk intact. No naked-eye evidence of pars anterior. Thyroid not examined; other organs appear normal.

Microscopic examination of the base of the brain shows complete removal of the anterior lobe. Pars intermedia cells appear active,

invading the pars nervosa in many places; acini contain an abundance of colloid, and hyaline bodies in unusual number fill the tissue channels of the pars nervosa and extend to the ventricular floor (Fig. 30).

These cases furnish additional evidence that the anterior lobe, from the standpoint of physiological equilibrium, is the most essential part of the gland, for after its removal the postoperative symptoms and average duration of life are the same as those following a total hypophysectomy.

3. *Consequences of Stalk Separation.*—The surgical division of the hypophyseal stalk, completely separating the gland from its infundibular attachment, is regarded by Paulesco as equivalent to a total or nearly total hypophysectomy. His contention is based on the results of 6 observations in which the stalk was divided and the gland left in the sella turcica. Three of these animals succumbed within 20 hours following the operation; the remaining 3 lived 6, 18 and 24 days, respectively. No mention is made, however, of the ultimate cause of death nor of the post mortem findings in any of these longer-lived animals of the series. The only protocol in full is that of an animal which succumbed in 20 hours, the hypophysis being found turgid, hæmorrhagic, and the cells in process of degeneration.

FIG. 25.—*Observation 25.* Photograph of animal 5 months after removal of posterior lobe. Animal very lively and playful (difficult to photograph). No appreciable symptoms consequent upon operation, with possible exception of erotomania.

We have made 5 observations of this type (*Table VI*). Two of the animals (*Observations 20* and *35*) succumbed with all the symptoms of cachexia hypophyseopriva, 1 on the tenth day and the other on the 24th day after operation. In *Observation 20*, a puppy, the gland was completely degenerated, making the procedure equivalent to a total removal; and in *Observation 35*, an adult male, the anterior lobe showed but few cells which retained normal staining reactions. *Observation 83* (Fig. 26), also an adult, was sacrificed on the 28th day, owing to symptoms of distemper, and at autopsy a large part of the anterior lobe was found still viable. *Observation 90*, a puppy, was sacrificed on the 12th day, while in a normal condition for the purpose of studying the tissues, and *Observation 33* was successfully tided over a period of threatened cachexia hypophyseopriva by glandular injections. The protocol of this case follows:

OBSERVATION 33. ***Separation of hypophyseal stalk. Symptoms of cachexia. Recovery after injections. Sacrificed after 5 months.***

***December 18, 1908.*** Adult male fox-terrier. ***Operation:*** Usual procedure except that the infundibular attachment was merely divided, leaving the gland lying detached in the sella turcica. No operative complications; good recovery from ether.

***December 19.*** Lively and in good condition but very vicious. Temperature 37.2° C.; respiration 14. Urine 880 cc.

***December 20.*** Taking solid food. Pulse 120; respiration 12; urine 935 cc.

***December 21.*** Temperature 38.1° C.; pulse 132; respiration 18, urine 950 cc., no sugar.

***December 26.*** Takes nourishment well but is losing weight. Urine 730 cc.

***December 29.*** Rapidly losing weight. Temperature 38.8° C.; pulse 144; respiration 10.

FIG. 26.—*Observation 83.* One month after stalk separation. Characteristic attitude (incurvation of tail and humping of back) with onset of cachexia hypophyseopriva, precipitated by attack of distemper.

***December 30.*** Onset of definite symptoms of cachexia hypophyseopriva. Given subcutaneous injection of 10 cc. of a prepared 1 per cent solution of anterior lobe of the pig.

***December 31. Injection repeated.*** Temperature 39.2° C.; pulse 128. Animal much brighter; restless.

***January 1 to February 4, 1909.*** During this period *injections* of anterior lobe extract (pig or ox) were given almost daily, 20 in all. Improvement was slow but definite, despite an attack of distemper(?) lasting for about 10 days, after January 4. During the injections there was a more or less constant pyrexia of a degree or so; they were all well tolerated and produced no abscesses.

Marked improvement set in toward the end of January and the injections were discontinued February 4.

***February 4 to March 1.*** A continued gain in weight during this period. Condition excellent, though an occasional slightly subnormal temperature.

***March and April.*** Has been in paddock with other animals.

Apparently normal in all respects, though growing fat. There was a gain of 4 pounds in weight in the last month.

*May 15.* Has shown no further symptoms. Remains well and fat. Temperature 38.5° C.; pulse 100; weight 18 pounds. Sacrificed on this date.

*Autopsy:* The hypophysis is represented by a fibrous tag adherent to the infundibulum. Naked-eye appearances of all organs normal, except the thyroid glands, which seem hyperplastic. *Microscopic:* The hypophysis is more or less embedded in scar-tissue which adheres to the floor of the third ventricle. Such of the glandular tissue as remains is relatively small in amount, but there are areas of normal appearing anterior lobe cells, a few of the acini containing colloid, there being one large colloid cyst. The sinusoidal vessels are much dilated.

The posterior lobe is more normal in size, but the pars nervosa is invaded by pars intermedia cells, which are large and seem hyperplastic (Fig. 27). There is an over-abundance of hyaline throughout the pars nervosa and many colloid cysts in its epithelial investment (Fig. 28).

The abdominal and thoracic organs, liver, spleen, kidneys and lungs, are normal. The *ductless glands* show: Testes; complete degeneration of spermatogenous epithelium, no spermatozoa, increase in interstitial tissue, no Leydig's cells apparent. Thyroid: colloid goitre; no active hyperplasia. Thymus: no recognizable change. Adrenal: normal.

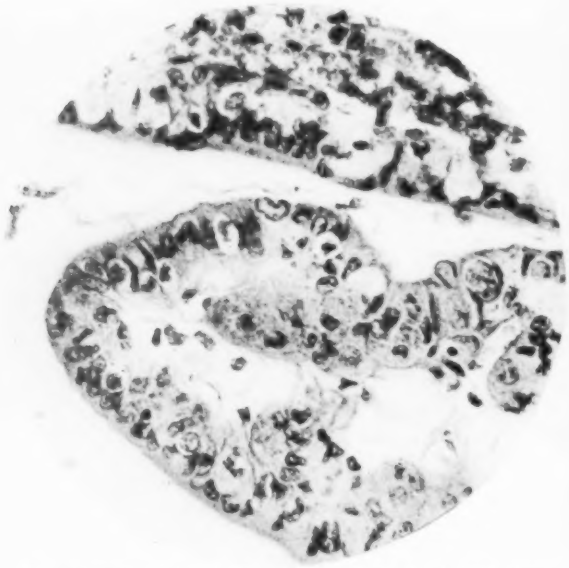

FIG. 27.—*Observation 33.* Activated cells of pars intermedia (hyperplasia?) after stalk separation.

The autopsy findings in this group are of especial interest, since they show that after separation from the base of the brain the structure, very much like a transplanted gland often degenerated, in large part, yet may retain enough viable cells to support life. It becomes reattached futhermore to the stump of the recently divided infundibulum and though slightly displaced from its former median position, as it was in all of our cases, it may nevertheless resume its normal function. The resultant condition, so far as the anterior lobe is concerned, is almost the same as if this portion of the gland had actually been removed and then reimplanted like a graft, for its circulation is almost entirely shut off.

The posterior lobe, on the other hand, though its blood supply should remain uninjured, nevertheless is seriously affected in another way; for, if we are to believe Herring's views, it discharges through the stalk and its secretion consequently will be dammed back by the resultant scar. In this connection the glandular blood supply and the presumed method of secretory discharge for the 2 portions of the gland deserve a brief description.

(a) *The Blood Supply of the Pituitary Body.*—Unreported studies made in this laboratory by Dr. G. J. Heuer and Mr. W. E. Dandy largely confirm, for the canine gland, the statements of Herring[21] in regard to its vascular supply in the cat. The arterial supply of the pars nervosa enters the posterior pole of the gland at the point of slight attachment encountered in the operation for removal. The anterior lobe, on the other hand,

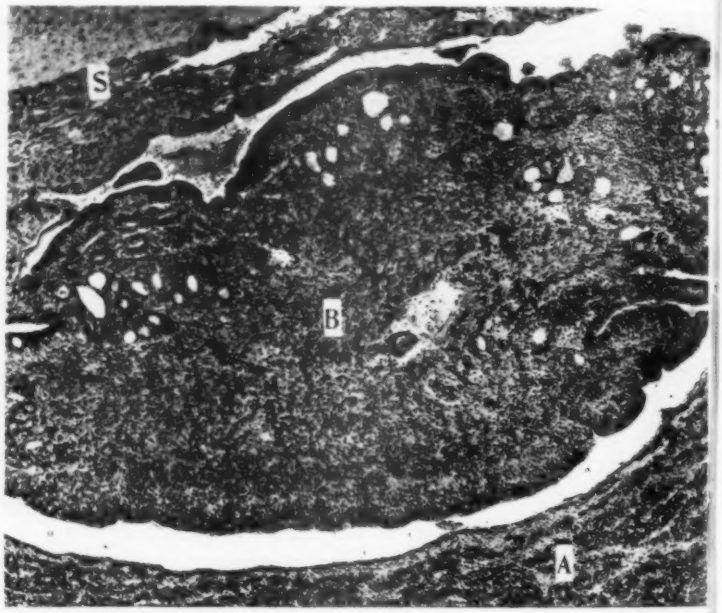


FIG. 28.—Pars nervosa of *Observation 33*, infiltrated with hyaline and containing colloid cysts after stalk separation. Anterior lobe remains normal. *A*, anterior lobe; *B*, posterior lobe; *S*, line of stalk separation.

receives its supply from small vessels which pass down the infundibular stalk and break up abruptly into the large sinusoidal spaces characterizing the blood vessels of this portion of the gland. There seems to be no free anastomosis between these systems.

Separation of the stalk consequently will shut off the direct blood supply to the pars anterior in many cases, almost as effectually as though the structure were actually taken from its bed. Thence arises the analogy between this operative measure and a favorable reimplantation elsewhere of this portion of the gland after its removal. Paulesco pointed out that in one of his cases at least, there was extensive degeneration of the pars anterior cells—just such a degeneration as we have

[21] P. T. Herring: The histological appearances of the mammalian pituitary body. *Quart. J. Exper. Physiol.*, 1908, II, 154.

seen in almost all of our transplants, and in one of these stalk separations (*Observation 20*) both lobes were almost completely degenerated, owing to accidental severance of the vessels to the posterior lobe when the stalk was being freed before its division.

That a large portion of the gland may retain its vitality, however, is evident from the condition found in *Observations 33* and *99* (Fig. 28); and in the protocol (*Observation 33*) just given, although it is probable, in view of the threatened cachexia hypophyseopriva symptoms, that the amount of functionating tissue was temporarily insufficient, nevertheless this period was tided over by injections. We shall see that it is possible to tide over a similar critical period after nearly total (anterior lobe) removals by glandular administration in one form or another.

(b) *The Question of Posterior Lobe Secretion.*—In describing the histological appearances of the posterior lobe in the cat, Herring calls attention to the peculiar faintly acid-staining "hyaline bodies" which are to be seen in the pars nervosa and appear to be making their way upward in the loose tissue channels toward the infundibulum. He came to believe that

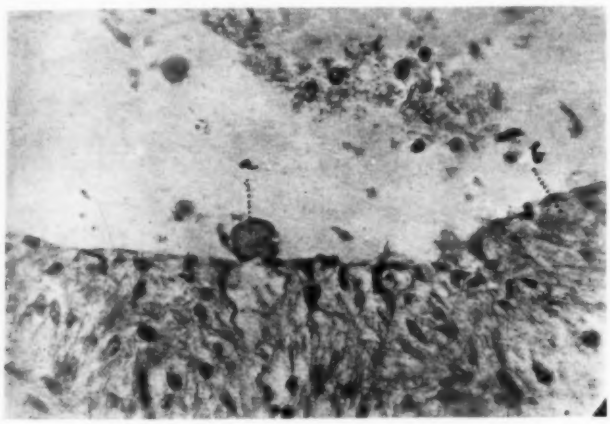

FIG. 29.—Hyaline bodies in *Observation 98* at infundibular floor; (*b*) before discharge, (*a*) after discharge. (Were it not a fairly common picture (*a*) might be considered an artefact.) (*c*) hyaline debris in ventricular cavity.

these bodies actually represent the secretion of this part of the gland, and they certainly occur in the situation in which the active principle has been demonstrated to lie.

The conditions are the same in the canine hypophysis, and we agree with him that the histological appearances point strongly toward the fact that this is an actual secretion and one which appears to be a product of activity of the cells of the epithelial investment (pars intermedia). The material seems to pass toward the infundibulum and in many cases may actually be seen passing into the cavity of the third ventricle (Fig. 29).

Certain of our surgical experiences, too, seem to lend direct support to Herring's hypothesis based on the study of normal tissues, and the more we have studied the posterior lobe in various post-operative conditions the more we have been inclined to accept his views. A great excess of the hyaline bodies is found in the tissues of many of our animals (Fig. 29a), and particularly in the stalk separations (as might be expected on the basis of this hypothesis) the pars nervosa may be crowded with them (Fig. 30).

It would appear that these hyaline globules take their origin from the cells of the pars nervosa, and indeed they actually resemble wandering cells, for in those bodies which lie nearer the epithelial investment ghosts of nuclei which apparently become extruded may often be made out (Fig. 31). In many conditions there seems to be an actual invasion of the pars nervosa by normal appearing cells, which gives an appearance akin to the tissue invasion by the cells of an epithelioma and one which is very often seen in the glands of adult man. Ordinarily, however, normally staining pars intermedia cells are not to be found far from the epithelial investment.

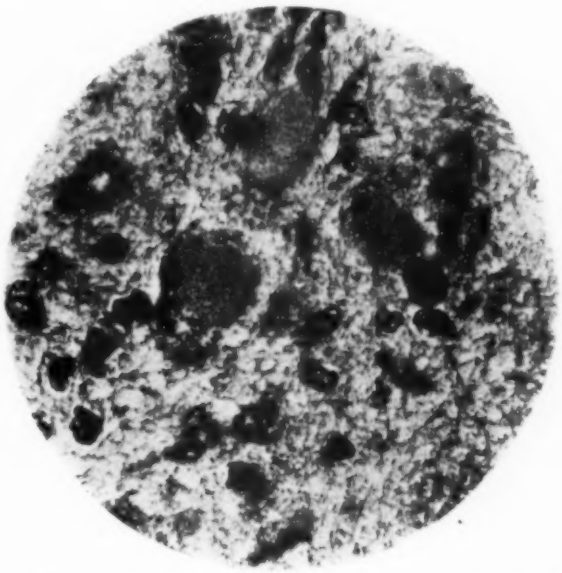

FIG. 29a.—Showing hyaline in pars nervosa of normal animal after glandular transplantation.

It was first pointed out by Howell that the blood pressure raising substance of the posterior lobe is limited to the pars nervosa, and we have failed to obtain any pressor response from injecting pars intermedia extract carefully prepared in the laboratory from the fresh glands of the pig. Neither does the true colloid secreted by the pars intermedia seem to contain the active principle, for the injection of the contents of large colloid cysts (bovine and human) has proved negative in our hands. It would seem probable, therefore, that the pars nervosa must in some way activate these hyaline bodies (at least if they are in any way related to the glandular colloid) during their passage toward the infundibular cavity.

These seem to be definite pathways for the "secretion" in the loose tissue spaces between the ependymal cell prolongations, and in cases of total or nearly total removal streaks of hyaline bodies are often seen passing through the nervous

tissue and extending from the remaining hyperplastic tags of pars intermedia up to the ventricle. Particularly after a stalk separation the posterior lobe may be found packed not only with colloid, but with these hyaline bodies as well (Fig. 28), and we are under the impression that the glands of individuals who have been afflicted with an obstructive hydrocephalus show much the same condition, and for the same reason—a matter to be considered on another occasion.

If these conjectures as to the secretory nature of the hyaline bodies, their origin from the pars intermedia, their activation during their passage through the pars nervosa, and their ultimate discharge into the cerebro-spinal fluid are to receive confirmation, they will represent a hitherto unrecognized form of glandular activity and a most bizarre outlet for its secretory products.[22]

The products of anterior lobe secretion, judging from the topographical arrangement of the cells along the thin-walled blood sinuses, probably enter the blood stream directly, and in certain pathological states one may even find the peculiar anterior lobe colloid within the vessels themselves. Colloid, however, does not seem to be the normal form of pars anterior secretion, and pathologists are as yet undetermined as to whether there may not be various forms of cellular activity corresponding to the 3 types of cells, acidophiles, basophiles and neutrophiles. Certain observations of our own favor the view advanced by Erdheim, that each of the 3 types possesses a differing function rather than that each variety represents merely a differing stage of cellular activity.

FIG. 30.—Showing channels in posterior lobe crowded with hyaline bodies (a few of them indicated by *x's*) after stalk separation.

[22] This is not, however, so bizarre when we realize how closely the cerebro-spinal space is connected with the blood stream; for the cerebro-spinal fluid, contrary to the usual interpretation of its function, seems to have a constant circulation and ready escape by way of the dural sinuses directly into the venous blood stream.

4. *Partial Removals of the Anterior Lobe.*—Hitherto, as has been pointed out, experimental removal of the hypophysis has had for its main object the determination of the essentiality or otherwise of the structure, and although opinions have differed, it is to be hoped that our confirmation of Paulesco's work will help to answer the question in the affirmative and show, at the same time, that it is the anterior lobe which is essential to life. Our predecessors in this work, however, have practically made either no comment (cf. *Table I*) on the late consequences of partial removal or else have denied (even after total removal) that any symptoms supervene.

One of the adult "partials" in Paulesco's series to which we have referred, lived for a year, became mangy, and died in a state of coma after "catching cold." This animal (*Expérience LXIII*), a male adult, gained in weight, as shown by the protocol, and had an occasional subnormal temperature. This apparently was not regarded as an evidence of hypopituitarism, as Paulesco concludes:

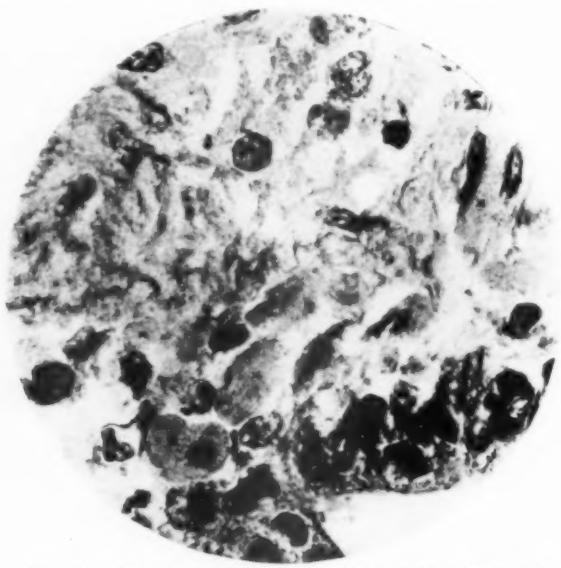

FIG. 31.—Showing edge of pars intermedia discharging hyaline bodies into pars nervosa (*x's*).

Aucun symptôme particulier et caractéristique ne traduit cette insuffisance relative du fonctionnement de l'organe pituitaire à la suite de l'hypophysectomie presque totale. L'animal se comporte absolument comme les animaux témoins, à hypophyse intacte..... Il est à noter que, chez les animaux dont la survie a été longue (5 mois, un an), ancune modification trophique appréciable n'est survenue au niveau des extrémités (museau, membres).

It was not until comparatively late in the course of the 1908-1909 series that our attention was called to peculiar and unmistakable alterations in some of the animals which had been kept under observation for weeks or months, a number of whom were even regarded surgically as presumptive "totals"—a fact which kept us long uncertain as to the actual essentiality of the gland, for the matter could not be settled for this particular group of cases until the final microscopic examinations were

made. Indeed, in one of the presumed totals (*Observation 98*) which was kept over until the present year, this final test of totality was only recently made, though our experience had made us sufficiently confident of finding a viable fragment in this, as we had in all other long-lived cases.

These unmistakable states of hypopituitarism to be described, we regard as far the most important outcome of our year's work, for they serve to throw light on the corresponding clinical conditions in man which have just begun to receive attention through the articles of Fröhlich, Frankl-Hochwart, Brissaud and others, but which could not have been suspected as being due to glandular inactivity of the pars anterior without these suggestive experimental states.

To throw further light on this aspect of experimental hypophysectomy has been the chief object of the 1909-1910 experiments still in progress under the direction of Dr. Goetsch and it must suffice for this present report to recount our preliminary observations.

The following tables include 18 partial hypophysectomies, in 6 of which a part of the anterior lobe alone was removed, leaving the posterior lobe *in situ* (*Table VII*), whereas in the remaining 12 observations the pars nervosa, with its investment, was included in the partial extirpation (*Table VIII*). Although there was no striking difference in the post-operative symptoms shown by the individuals in these 2 groups, they are presented, nevertheless, in separate tables for the purpose of further emphasizing the physiological importance of the pars anterior, for the results seem to be practically the same with or without removal of the posterior lobe. This might have been expected could we have foretold (1) that a *complete* extirpation of the anterior lobe would be invariably fatal, even when the posterior lobe and its epithelial investment are left intact, and (2) that the posterior lobe alone could be removed and the animal survive for an indefinite period.

(a) *Effects of Partial Removal of the Pars Anterior, Leaving the Posterior Lobe in Situ* (*Table VII*).—The operations in 3 (*Observations 29, 30, 31*) of these 6 animals were intended for adult total anterior lobe extirpations, but the unexpectedly long survivals, averaging 28 days, were accounted for by the post-mortem demonstration of viable, though microscopic anterior lobe fragments embedded in the scar-tissue. These may be compared with *Observations 61* and *66* of *Table VIII*, cases in which the posterior lobe was removed as well, the terminal symptoms not occurring until 60 and 37 days after the operation, a longer survival than in the fatal cases with retained posterior lobe.

The duration of life in the cases retaining these minute fragments, is proportionate according to Paulesco to the size of the fragment, but it would seem better to say that it is proportionate to its cellular activity rather than to its mere size. Favorable external circumstances, furthermore, are important, for accidental infections, exposure, digestive disturbances and what not may doubtless prove the determining element of sufficiency for in their absence an astonishingly minute fragment may serve the animal's physiological needs.

Of the other 3 cases of *Table VII, Observation 26* succumbed within the usual time to symptoms of cachexia hypophyseopriva, despite the retention of a minute anterior lobe fragment which, however, was found much lacerated and infiltrated with blood. *Observation 34* lived for many months, as did also *Observation 27*, the latter case being complicated somewhat by an associated thyroidectomy performed in the hope of accentuating the histological changes of the remaining fragment. Owing to this some of the symptoms suggestive of hypopituitarism—the gain in weight, thickness of skin, hypotrichosis and subnormal temperature—might have been ascribed to myxœdema. The microscopic studies of the fragment of *Observation 27* showed it to be small and completely enveloped in scar-tissue, but the individual cells were much enlarged, containing huge vesicular nuclei and an abundant protoplasm showing but few faintly staining eosinophilic granules—an appearance which we have come to regard as representing active hyperplasia (cf. Fig. 36). The posterior lobe was shrunken and almost entirely replaced with ingrowths of pars intermedia cells with an abundance of colloid and many hyaline bodies, comparable to the condition described in *Observation 33* (Figs. 27 and 28), a case of stalk separation. The ovaries were small and sclerotic and contained very few developing ovules.

Inasmuch as *Observation 34* was the first of the experiments in which the excessive adiposity was noted and as no attempt was made to modify the progress of the symptoms until the injections were made at the end of 6 months, the case deserves to be recorded in greater detail. An abstract of the protocol follows:[23]

OBSERVATION 34. ***Partial removal of anterior lobe with stalk separation; symptoms of hypopituitarism, adiposity, etc.; febrile reaction to injection of anterior lobe extract; sacrificed after 6 months.***

Adult female 14-pound fox-terrier.

*December 18, 1908. Operation:* Partial removal of anterior lobe; posterior lobe *in situ* though stalk separated. No operative complication and prompt recovery from anæsthetic.

*December 19.* Bright though inactive and very irritable. Takes milk and water. Urine 1200 cc., no sugar.

*December 24.* There have been no post-operative complications; wound has healed *per primam*. Animal taking solid food. Urine 1340 cc.

*January 24, 1909.* Has gained 3¼ pounds during the past month. *Weight* 17½ pounds (Fig. 32). Polyuria has persisted, varying between 980 and 1320 cc. Temperature occasionally slightly subnormal.

*February 15.* Though rather inactive the animal has shown a good appetite for the past 3 weeks. There has been considerable shedding of hair, but her coat is not rough and bristly as in some other of the more completely hypophysectomized animals. With the exception of the persisting polyuria, nothing unusual has been observed. Urine to-day 1260 cc., no sugar.

*March 4. Weight 19½ pounds.* Very sleek and fat, though fed on usual rations with control of same age. Appetite does not seem excessive.

*March 22. Weight 22 pounds*, a gain of 2½ in 18 days (Fig. 33). Urine 920 cc. Animal continues sleepy, dull and inactive. Temperature often slightly subnormal.

[23] This case is also recorded in full in Ziegler's Beiträge.

*May 10.* Since the last note has been allowed the freedom of the paddock with other animals. She has apparently not been in heat since the operation. Polyuria persists; urine to-day 1440 cc., no sugar. She is sleek, fat and inactive. *Weight 23 pounds.*

*May 20.* Replaced in metabolism case for the past 10 days; polyuria even more marked than heretofore, averaging 1620 cc.

*May 28.* Animal continues in cage. Appetite is fair, but she is not ravenous, as food is often left in her pan. She is inactive and sleeps much of the time. Temperature 36.5° C. (the first marked subnormal registration); pulse 128. Urine 980 cc., no sugar. Her *weight* to-day is 23¾ pounds, while that of a control bitch who has been kept under like conditions is only 16 pounds (Fig. 34).

*June 1.* Since the last note animal again turned in yard. There has been no sign of her being in heat. Polyuria persists. Urine 1140 cc., no sugar. *The total gain in weight has been 9¾ pounds—over 70 per cent increase.*

At this juncture, with temperature 38° C., pulse 136 and urinary output 880 cc., a subcutaneous injection of 10 cc. of boiled anterior

Fig. 32.—*Observation 34.* Adult fox terrier bitch. Photograph 36 days after operation, when striking gain in weight first began to be observed.

lobe aqueous suspension (ox)[34] was administered, leading to a marked febrile response to 40.6° C., and to an increase in polyuria, namely, 2400 in 24 hours. The pyrexia continued for three days with no local reaction at point of injection, and at the end of this time the animal was sacrificed.

*June 17. Autopsy:* The panniculus over chest and abdomen varies from 5 to 8 cm. in thickness: there is an especially marked accumulation of fat around the lower jaw and back of the neck. No local tissue reaction at site of injection.

*Mammary glands* and *nipples* are small and undeveloped.

*Paws* are small and free from fat. There are no apparent abnormalities in the long bones (no sections).

*Head:* The operative wound has healed perfectly. Brain and meninges appear normal. The remainder of the hypophysis is more firmly adherent than normal to the infundibular region and a considerable fragment of the anterior lobe is recognizable by its color.

*Neck:* Thyroids are firm, colloidal and slightly larger than normal; parathyroids prominent. No definite traces of thymus are seen.

*Thorax:* Lungs and pleura are normal.

*Abdomen:* Intestines and peritoneum are normal. The *liver* is obviously fatty, looking almost white on gross section.

*Kidneys, pancreas* and *adrenals* show no gross abnormalities.

*Ovaries* are small and buried in fat.

*Uterus* is infantile and is represented by a mere thread of tissue (hypoplasia).

Microscopic. *Base of Brain:* Serial sections through the infundibular region and hypophysis show that the gland, whose stalk was purposely separated at the operation, has become reunited to the base of the third ventricle in nearly normal position. The *posterior lobe* is markedly altered. There is no trace of the original *pars nervosa*, the entire lobe being filled with pars intermedia cells, many of them forming acini containing colloid, so that the condition resembles active thyroid tissue. The appearances are interpreted as due to stasis of posterior lobe secretion. A considerable fragment of the *anterior lobe* remains; it is very vascular, the blood sinuses being greatly dilated. The cell columns show many brightly-staining, small eosinophiles which line the blood vessels. The centers of some of the cell columns contain groups of nuclei with scant protoplasm which takes no stain (Kernhaufen of Rogowitsch).

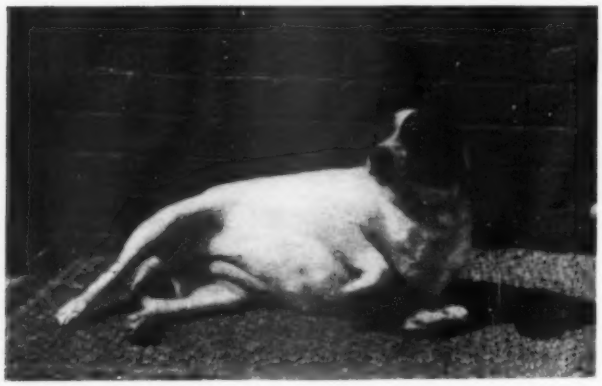

Fig. 33.—*Observation 34.* Ninety-two days after operation. Condition of adiposity well established. Note disproportionately small and delicate extremities.

*Thyroid:* Cells flat; acini distended with colloid.

*Liver:* Diffuse and marked fatty degeneration of all cells. *Myocardium* also shows fatty change.

*Pancreas* and *spleen* appear normal.

*Adrenal:* Marked vacuolization of cells of deeper layer of zona fasiculata.

*Ovaries:* Many developing ova which appear normal: 3 large irregular shaped areas made up of vacuolated chromaffine cells (abnormal corpora lutea?).

This was the first case in which we observed the symptoms which characterize certain tumors of the hypophysis of the type described by Fröhlich, a physiological explanation for which on the grounds of glandular deficiency has heretofore been impossible. The more noticeable alterations from the normal were the marked adiposity, abeyance of the sexual function, polyuria, sleepiness, and the tendency toward a subnormal

[34] Prepared by dissolving 1 gram of the dried powder of the anterior lobe of the ox in 100 cc. of distilled water, boiled.

temperature. Possibly the *most important incident of this history, however, was the thermic response to the injection of anterior lobe extract*—a part of the gland which under normal circumstances has long been known to give no reaction.

(b) *Partial Removal of the Pars Anterior Together with the Entire Posterior Lobe (Table VIII).*—This group includes 13 cases in which the posterior, as well as the greater portion of the anterior lobe, was removed. A number of them were considered to be "totals" at the time of operation. Three of the cases succumbed to cachexia hypophyseopriva. Of these, *Observation 43*, an adult, died on the 2d day. The minute fragment, though showing normal staining reactions, was found infiltrated with blood, and had the operation not been conducted in the winter months or had a timely injection or a transplant been used, recovery would have been possible.

*Observations 61* and *66* were puppies, also surgically regarded

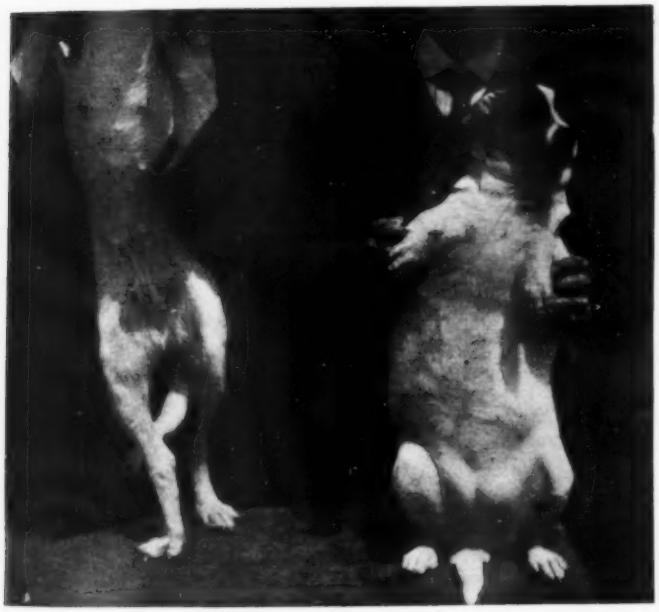

FIG. 34.—*Observation 34* (right), 153 days after operation, weight 23¾ pounds, a gain of 9¾ pounds. Control (left) kept under like conditions weighs 16 pounds.

as totals. The former, aside from a transient polyuria, remained well and gained in weight until on the 54th day it caught distemper, became somewhat lethargic, and with a fall in body temperature gradual symptoms of cachexia set in (Fig. 35) which led to death in 6 days. The clinical course of *Observation 66*, barring the infection, was in many respects similar. The animal was bright and lively for 2 weeks and gained 2¼ pounds in this interval. The onset of the terminal symptoms was most gradual, though characteristic in all features, and it was 24 days before death occurred, the body temperature having fallen to 17.5° C. before the end. In both of these cases a microscopic viable anterior lobe fragment was found (Fig. 36), and though insufficient to support life, nevertheless it can be seen that the usually abrupt terminal symptoms characterizing the "totals" were much prolonged.

In 3 of the other 9 cases, *Observations 49, 88* and *100*, the remaining fragments were likewise microscopic and their identification necessitated a careful search through the serial sections. The animals all showed temporary symptoms of postoperative cachexia, *Observation 100* being sacrificed while they were in evidence, for examination of the tissues. The other 2 recovered. One of them (*88*) was in good condition when sacrificed on the 12th day, and microscopic examination revealed a small fragment of anterior lobe surrounded by an organizing blood-clot. The anterior lobe cells were of the actively secreting type (Fig. 37), and it is a natural conjecture that the fragment was so damaged that for a few days after the operation it was functionally insufficient, but owing to restoration of its activity with hyperplasia, complete recovery of the animal followed. Analogous recoveries after the development of hypophyseopriva symptoms have been seen, as we have stated, after total hypophysectomies with immediate cortical implantation of the recently removed gland; and the histologic appearance of the transplants, in these cases also,

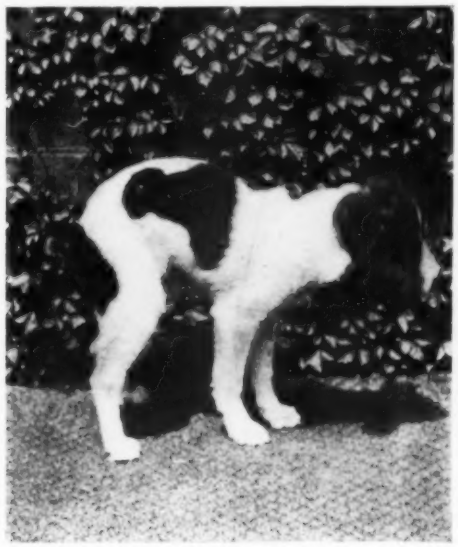

FIG. 35.—*Observation 61.* Presumed "total"; proven "partial." Photograph 52 days after operation. Note characteristic posture of early stage of cachexia hypophyseopriva precipitated by attack of distemper.

suggested an extreme degree of activity on the part of the cells of the anterior lobe.

*Observation 49* is in many respects similar to the above case. Apparently the entire gland was removed at operation, and for the succeeding 2 or 3 days the animal was lethargic, refused food and had a subnormal temperature. On the 4th day, however, the normal conditions became restored and the animal was sacrificed 17 days later. A microscopic fragment of anterior lobe was found with its cells almost identical in appearance with those of *Observation 88*. The thyroids presented definite hypertrophic changes, possibly compensatory ones since corresponding changes are said to occur in the pituitary body after primary removal of the thyroids. A further description of the

histological alterations of the pars anterior denoting what we regard as hyperplasia, must be deferred for a subsequent communication.

Fairly good fragments were present in *Observations 71, 80* (Fig. 8) and *81*. These 3 animals were sacrificed for tissue study after some weeks had elapsed, but before definite symptoms of chronic hypopituitarism had occurred, though they were gaining in weight.

*Observation 81*, a small female (Figs. 7 and 38), showed a gain of 2 pounds in the 34 days. These symptoms, however, were much more definite in the 3 animals (*Observations 54, 55* and *98*) allowed to survive a longer time. In *Observations 54* and *55* the fragments were large enough to be seen by the naked eye, whereas in *98* it was of microscopic size and the animal did not become fat.

FIG. 36.—*Observation 66 (Table VIII)*. Showing fragment of anterior lobe left after an hypophysectomy supposedly total. Fragment in active hyperplasia.

*Observations 54* and *55* are of especial interest, for, though adult males, they present many clinical similarities to *Observation 34* (*Table VII*) and are a striking illustration of a moderate degree of chronic hypopituitarism. *Observation 54* (Fig. 39) was an adult, mongrel, 16-pound, black spaniel, with possibly three-fourths of the anterior lobe removed. A post-operative polyuria appeared and persisted and in this case a transient glycosuria was observed (estimated from polariscopic readings at 1.65 grams of glucose to the liter). The animal gained from 16 to 27 pounds in the 3 months following the operation, became sexually impotent (or indifferent), had an occasional subnormal temperature, and gave a definite thermic response (from 38.6° C. to 41.8° C.) as well as blood pressure and respiratory ones to the intravenous injection of 3 cc. of the standard 1 per cent aqueous solution of anterior lobe extract.

The symptoms in *Observation 55* were exactly the same but with a more persistently subnormal temperature, often as low as 37° C. even during warm weather (June), and a marked thermic response from 38° to 42.5° C. in 2 hours after the test anterior lobe injection. It was in this case that the post-operative testicular atrophy (Figs. 40 and 41) was for the first time strikingly called to our attention. The protocol follows:

OBSERVATION 55. ***Partial hypophysectomy; transient polyuria; atrophied genitalia; impotency (?); adiposity; sacrificed 10½ days after operation.***

Adult male fox-terrier, 2 years of age, weighing 17 pounds.

*March 3, 1909. Operation:* Supposedly a total removal. No post-operative complications.

*March 4.* Animal active and seems brighter than is usual for an adult animal the day after a total hypophysectomy; drinks water and milk greedily. Temperature 38.5° C.; pulse 165, irregular. Urine for 24 hours preceding operation 200 cc. (no sugar); for 24 hours following, 1100 cc. (no sugar).

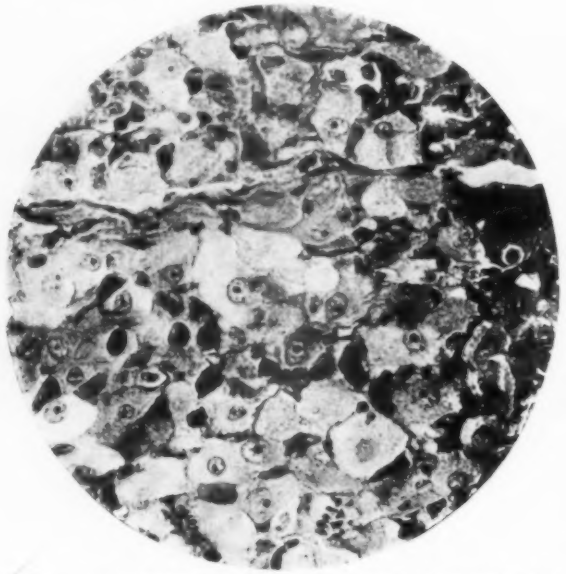

FIG. 37.—Showing character of change (hyperplasia?) seen in many anterior lobe fragments. Dark staining acidophiles, few in number; most of the cells being enormously enlarged and staining indifferently.

*March 5.* Urine 870 cc., no sugar.

*March 6.* Wound healing perfectly. Animal has shown no symptoms of cachexia hypophyseopriva. Appetite continues good. Temperature 38.5° C.; pulse 76, very irregular. Urine 230 cc., no sugar.

*March 7 to 16.* Continues in very good condition; eats well; weight 18½ pounds. Temperature 38.4° C.; pulse 88, irregular. Urine 320 cc., no sugar.

*April 10.* In very good condition. Temperature 37.8° C. (slightly subnormal); pulse 98, regular. Urine 400 cc., no sugar.

*May 1. Weight* 21½ pounds—a gain of 4.5 pounds since operation. Bright and lively. Temperature 38.4° C.; pulse 88. Urine 360 cc.

*May 1 to June 4.* During this period has been allowed freedom of paddock with other animals. Does not seem sexually normal (will take no notice of a bitch in heat when placed with her). Hypoplasia of the external genitalia has become obvious (Fig. 40).

*June 5.* Temperature 37.9° C.; pulse 76. Urine 770 cc. (slight polyuria again).

*June 12.* Polyuria continues; urine 840 cc., no sugar. Seems to be sexually impotent. Temperature 38.2° C.; pulse 92, irregular.

*June 15.* Bright and playful. *Weight* 23 pounds—a gain of 6 pounds since the operation (Fig. 41). Temperature 38.4° C.; pulse 92. Urine 800 cc., no sugar.

On this date an *injection* of 3 cc. 1 per cent solution of anterior lobe (ox) was given intravenously to investigate the thermic blood pressure and respiratory reactions under these conditions of hypopituitarism. Immediately following the injection there was a slight rise in blood pressure (as was seen in 4 other instances of a similar anterior lobe injection in animals with a partial removal) and a marked respiratory attack (respiration from 40 before to 300 after injection). *Two hours* after injection the animal's temperature had risen to 42.5° C., being 3.8° C. above the normal.

Animal was sacrificed 3 hours after the injection.

*Autopsy:* Body unusually fat. Panniculus measures from 4 to 5 cm. in thickness over chest and abdomen. Crainal wound healed perfectly. Brain and meninges normal. To the naked eye there is a small tag of tissue in the hypophyseal region which presumably contains an interior lobe fragment.

*Testes* firmer than usual and less than half normal size. Other organs appear normal.

*Microscopic:* In the hypophyseal region there is a strip of active pars intermedia cells, a portion of the cleft and a small fragment of anterior lobe apparently in hyperplasia: also an appearance in the ventricular wall suggestive of ependymal hypertrophy. The

FIG. 38.—*Observation 81.* Adult multipara. Nearly total removal. Photograph 10 days after operation. Gaining in weight.

glandular fragment is embedded in scar-tissue which has undergone a peculiar fatty change.

*Testes:* Complete degeneration of spermatogenous cells: no spermatozoa. *Adrenals:* Extreme vacuolization of cells in lower layer of zona reticularis; hyperplasia (?) of medulla. *Thyroid:* Acini distended with excess colloid; lining cells flat. Liver, kidneys and other organs practically normal.

These cases, *Observations 54* and *55*, together with *Observation 34* (*Table VII*), are the most representative illustrations in our 1908-1909 series of the effects of long-enduring hypophyseal deficiency of moderate degree. Further advances in this direction have been made in the 1909-1910 series, but as studies of this kind necessarily cover many months, the report of these more complete observations must be deferred until all the tissues can be obtained and thoroughly studied.

Owing to the long survival a final case from *Table VIII* deserves mention.

This animal (*Observation 98*), a young black and tan bitch, surgically a presumed "total" was kept under observation for 9 months —the only one of our series allowed to survive for this length of time. She recovered promptly from the operation (June 11, 1909) and showed the usual polyuria but no symptoms of cachexia hypophyseopriva during the unfortunately short period of observation before the summer vacation.

In October she was found with a thick, dry skin and hypotricosis, and though not noticeably fat she had gained considerably in weight. Up to March, 1910, when sacrificed, she apparently had never been in heat. Her carbohydrate tolerance was estimated (70 grams cane sugar) and an anterior lobe injection test was made, the temperature rising from 38.8° to 40° C. in 2 hours, with the usual gradual return to normal. A control animal gave no thermic response.

FIG. 39.—*Observation 54.* Two months after partial hypophysectomy. Animal dull, sleepy, impotent, with 10-pound gain in weight.

At *autopsy* a microscopic fragment of anterior lobe was found (Fig. 42); the thyroids were colloid in character, suggesting former hypoplasia (Marine); the infantile uterus was represented by mere threads of tissue and the ovaries were entirely undeveloped.

5. *Hypopituitarism.*—Just as in cretinism *versus* myxœdema and gigantism *versus* acromegaly—states which differ only in so far as the process has originated either before or after adolescence, so apparently may we have 2 types of hypopituitarism. The adult animals become adipose and sexually degenerate, whereas the young likewise often grow fat but they remain undersized (as Fichera found to be the case with chickens), and sexual infantilism persists. Polyuria, glycosuria, a slightly subnormal temperature, changes in the nutritional condition of the skin and its appendages, with hypotricosis and occasional

FIG. 40.—*Observation 55.* Two months after partial hypophysectomy, when genital hypoplasia first became apparent. Gain of 4 pounds in weight (cf. Fig. 41.)

FIG. 41.—*Observation 55* (left), 3 months after operation, showing gain of 6 pounds and extreme genital atrophy; (right) normal control of same age.

FIG. 42.—Microscopic pars anterior fragment from *Observation 98 (Table VIII).* *a*, infundibular wall with few pars intermedia cells; *b*, chiefly pars intermedia cells; *cc*, cicatricial tissue; *d*, fragment of pars anterior.

FIG. 43.—Showing (right) a puppy's liver mottled by extensive focal necroses after 13 consecutive subcutaneous injections (each representing the emulsion of a single entire canine gland) contrasted with normal liver of control puppy (left) from same litter.

transient œdemas, are usual symptoms. Psychic disturbances have been common, sometimes with inactivity and sleepiness, sometimes the reverse with a restless playfulness. Many of the animals are more irritable than normal.

Further data in regard to these matters must be kept for our 1909-1910 reports, which will not only more clearly show the effect of the partial hypophysectomy upon growth, but will also throw further light on the histological alterations in the other ductless glands, of which we had only begun to have glimmerings, restricted largely to the occasional acute thyroid hyperplasia after total removal, and the atrophy of the spermatogenous epithelium in the long-lived adult males.

6. *Transplantations and Injections Associated with Partial Removals.*—We have mentioned in an earlier section the fact of having made 23 experiments with glandular grafts in the hope of setting aside or modifying the symptoms of cachexia, which are inevitable after total removal of the gland. Only 7 of the hypophysectomies, however, in which the transplants were made, were subsequently proven to be "totals," minute anterior lobe fragments having been found at the base in all of the other 16 cases. Many of the remaining 16 animals showed transient post operative symptoms of cachexia from which the majority recovered, and almost all of them were sacrificed after 2 or 3 weeks—too early for definite signs of hypopituitarism to have manifested themselves—for the purpose of studying the condition of the transplanted tissue.

The grafts in most instances showed a peripheral zone containing viable cells, but as their centers were always entirely degenerated we placed little trust in the functional capabilities of the comparatively small normal residue for at the time of making these grafting experiments we were unaware that a microscopic fragment might support life if the early symptoms could be tided over, as doubtless they were in many instances by these transplants. In one of the puppies, indeed, a secondary wave of cachexia hypophyseopriva symptoms appeared a month after the hypophysectomy, at which time the removed tissue had been implanted under the rectus muscle: a second (homogeneous) gland was immediately ingrafted, with prompt improvement in the symptoms and ultimate recovery. Doubtless, in view of our experiences with the 1909-1910 series, subcutaneous injections of the boiled emulsion of the anterior lobe would have answered the same purpose.

Among the *Observations* not included in the 8 tables which accompany this paper, the purely surgical results were confused in many instances by *injection experiments* with the extract or emulsion of one or another subdivision of the hypophysis prepared by ourselves either from the aseptically removed canine gland, or from fresh glands of the pig or ox secured from the abattoir.[35] It was found that a suspension of the powdered posterior lobe does not lose its activity on boiling, and apparently the same is true of the pars anterior as well, if we can rely on the thermic reaction (cf. below) as a test. An aqueous suspension of the dried and powdered gland can therefore be sterilized before injection.

To briefly summarize our experiences: Repeated injections of the entire gland, in the attempt to reproduce hyperpituitarism, was soon found to cause rapid loss of weight both in puppies and adults; and it was learned that this nutritional disturbance was due to the inclusion of posterior lobe in the preparations. It was in these animals that we first met with the extreme degrees of hepatic degeneration subsequently found under other of the experimental conditions. The external appearance of one of these mottled livers when contrasted with the normal, shows how extreme the degeneration may be (Fig. 43). This same lesion, is must be added, with no accompanying histologic change in the kidneys, has been found in a number of our hypophysectomized animals without injections. It

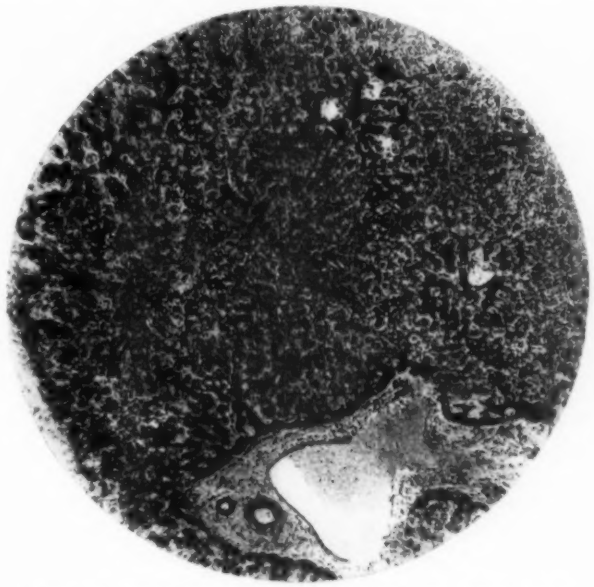

FIG. 44.—Showing extensive liver necrosis after whole gland injections × 60 diams. (cf. Fig. 43).

appears to be a form of extensive central?) necrosis (?) (Fig. 44).

The subcutaneous administration of pure anterior lobe preparations, on the other hand, caused no such disturbances, and in 1 instance a normal puppy was given daily injections over a period of 3 months without apparent ill (or other) effect. We consequently limited ourselves to the extract of pars anterior, not only for the attempted reproduction of hyperpituitarism, but also, and with evident success, as a therapeutic measure in substitution for the more elaborate transplantation procedure as a means of tiding over periods of threatened cachexia hypophyseopriva in the cases of "almost total" hypophysectomy. It was in the course of these undertakings that we first observed:

7. *The Thermic Reaction.*—Next to the experimental demonstrations of a recognizable symptomatology for states of hy-

[35] Mr. F. M. Bell, of the Armour Company, has kindly supplied us from time to time with large quantities of fresh bovine glands, and this company has now put upon the market the dried extract of both anterior and posterior lobes separately.

popituitarism, possibly the most important thing which we have stumbled upon during our studies of these animals is the occurrence of a thermic response to injections of boiled aqueous emulsion of the pars anterior in cases of anterior lobe deficiency (cf. protocols of *Observations 33* (*Table VI*), *34* (*Table VII*), *54*, *55* and *98* (*Table VIII*). This has been repeated without failure in practically all of the later anterior lobe "partials" of our own as well as in those of Dr. Goetsch's series; and judging from a few cases of suspected hypopituitarism in man, it appears to hold true for the human as well—a matter which may prove to be of value for the diagnosis of clinical cases. Needless to say, the reactions were controlled, with negative results, by posterior lobe injections in the partially hypophysectomized animals, as well as by injections of the emulsion of one or the other lobe in normal individuals.

The results given in this paper represent merely a stage in our investigations, and necessarily many suggestive topics have been merely touched upon. Further data in regard to the injection experiments as well as to those with glandular feeding, and a more detailed discussion not only of the histologic appearances of activation in the cells constituting the retained fragments, but also of the post operative alterations in the other ductless glands, must be left for the confirmation and additions of the 1909-1910 experiences.

## VI. Summary.

Past investigations have led to no unanimity of opinion in regard to the physiological essentiality of the hypophysis cerebri. Thus, of the two most important studies those of Paulesco favor, while those of Gemelli oppose, the view that loss of the gland is necessarily fatal.

Accurate and uncomplicated removal of the gland from the dog—the animal most suited to these investigations—was impossible before the introduction of Paulesco's subtemporal procedure with its principle of cerebral dislocation, and many of the symptoms described by authors before him must in large part have been due to operative trauma, or, in the absence of symptoms, to incompleteness of removal.

We find, in agreement with Paulesco, that a state of apituitarism due to the total removal of the hypophysis leads inevitably to the death of the animal, with a peculiar and characteristic train of symptoms (cachexia hypophyseopriva). That these symptoms are not due to surgical trauma or postoperative complications is evidenced by the facts (1) that the same operative manipulations leaving the hypophysis in place and omitting the single step of removal leads to no symptoms whatsoever, and (2) that incomplete removals produce no immediate disturbances.

However, even in the case of adult animals death need not occur after a total removal as promptly as Paulesco claimed; whereas puppies may remain in an apparently normal condition for at least 3 weeks before the terminal phenomena appear.

These same symptoms, after the same intervals of time, follow the removal of the entire pars anterior alone, even though the posterior lobe remains in place. On the other hand, removal of the posterior lobe (necessarily leaving a small amount of pars intermedia) not only leads to none of the manifestations of cachexia hypophyseopriva, but does not appear to affect the physiological balance of the animal in any symptomatic way, unless the convulsions and excessive sexual activity which have been seen in a few cases can possibly be ascribed to its absence.

Separation of the hypophyseal stalk, owing to circulatory disturbances is comparable either to a partial hypophysectomy or to a total removal with immediate reimplantation of the excised tissue elsewhere in the body. The gland becomes reattached and the pathways for posterior lobe secretion (supposed to traverse the pars nervosa on its way to the infundibular cavity) may become obstructed by the scar, leading to an accumulation of "hyaline" within the channels of the pars nervosa.

Definite constitutional disturbances which we may regard as manifestations of hypopituitarism have been observed after partial (anterior lobe) removals in a number of animals kept under observation for long periods of time. The most striking feature is a state of adiposity accompanied by (or resultant to?) a secondary hypoplasia of the organs of generation in adults or by a persistence of sexual infantilism in case the primary hypophyseal deficiency antedates adolescence. Polyuria, glycosuria, alterations in the skin and its appendages, (such as œdemas and hypotrichosis) the tendency to a subnormal body temperature, and psychic disturbances are more or less frequent accompaniments—all of them symptoms which occasionally occur with states of adiposity and of sexual infantilism in man, in company with certain pituitary body tumors—states, therefore, which presumably are due to hypophyseal (anterior lobe) deficiency.

Animals, in states of hypopituitarism, appear to have a lowered resistance to infection, exposure or disease, conditions which are apt to precipitate the onset of cachexia hypophyseopriva.

It has been possible, by glandular transplantations or by injections of anterior lobe emulsion, definitely to prolong the life of animals after total hypophysectomy, and likewise to tide over periods of threatened cachexia hypophyseopriva in animals retaining anterior lobe fragments which temporarily may be physiologically insufficient.

Boiled anterior lobe emulsions appear to elicit a characteristic (anaphylactic?) febrile response when injected subcutaneously in states of experimental hypopituitarism.

TABLE II.—ADULT TOTAL HYPOPHYSECTOMIES.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Sugar. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 6.*—Oct. 3, 1908. Fox terrier; male; complete removal in fragments; injury to temporal lobe. | October 4.<br>October 5.<br>October 6.<br>October 7.<br>October 8. | 38.4° C.<br>38.2<br>38.2<br>38.2<br>30.1 | 168<br>144<br>120<br>124<br>120 | ..... | ..... | Rotary progression (due to unilateral injury of the pyramidal tract); lethargy; arching of back; general muscular tremors; became comatose on 5th day after usual symptoms. | 5 days. | Wound healed per primam; under surface of left temporal lobe lacerated and hæmorrhagic. Interpeduncular region occupied by a blood-clot; no evident remains of the hypophysis. Thoracic and abdominal organs appear normal.<br>*Microscopical.*—A few pars intermedia cells remain; no trace of anterior or posterior lobes; organizing blood-clot. |
| *Observation 12.*—Oct. 29, 1908. Dry, clean exposure; no bleeding; entire gland removed in one piece; no injury to temporal lobe. | October 30. | 28.0 | Not palpable; heart-rate 40 to minute; very irregular. | Anuria. | ..... | Animal never entirely recovered from the anæsthetic; gradually became comatose after usual symptoms. | 36 hours. | Brain and meninges appear normal; very small blood-clot at base; no evidence of anterior or posterior lobe. Lungs normal; abdominal organs appear normal.<br>*Microscopical.*—A few pars intermedia cells remain; infiltrated with blood and leucocytes. No anterior-lobe cells seen (serial sections). |
| *Observation 14.*—Nov. 2, 1908. Dry, clean approach; gland removed in one piece; no hæmorrhage; floor of 3d ventricle torn out, with escape of cerebro-spinal fluid. | November 3.<br>November 4.<br>November 5.<br>November 6. | 35.0<br>33.8<br>33.2<br>26.0 | 120<br>116<br>120<br>Not palpable. | 120 cc.<br>60<br>80<br>Anuria. | ..... | Promptly recovered from anæsthetic; on following day was lethargic; if aroused will walk unsteadily around the room; arching of back; comatose on 3d day; temperature subnormal; reflexes retained; pulse feeble and irregular. | 4 days. | Base clean, no blood-clot. Areas of bronchial pneumonia; abdominal organs appear normal.<br>*Microscopical.*—Floor of 3d ventricle open (cf. Fig. 19); no evidence of pars intermedia or anterior-lobe cells. Thyroid normal. |
| *Observation 22.*—Nov. 27, 1908. Gland removed in fragments; constant venous oozing at base; no injury to temporal lobe. | November 28. | 32.0 | 60 | Anuria. | ..... | Recovered from anæsthetic with usual promptness; soon became comatose; infrequent, deep respirations; slow, irregular pulse and subnormal temperature; death at 8 p. m. | 18 hours. | Brain under considerable tension; cerebro-spinal fluid bloody; large clot in interpeduncular region, extending backward to foramen magnum.<br>*Microscopical.*—No evidence of hypophyseal cells (serial sections). |
| *Observation 28.*—Dec. 4, 1908. Dry, clean operation; gland removed "in toto"; floor of 3d ventricle torn away, followed by cerebro-spinal fluid. | Dec. 5 (9 a. m.)<br>(6 p. m.)<br>December 6. | 38.7<br>35.2<br>26.0 | 168<br>152<br>48 | 230<br><br>Anuria. | ..... | Promptly recovered from anæsthetic; 12 hours later was semicomatose; temperature fell 3.5° C. during the day; comatose on 2d day; rectal temperature 12.5° C. below normal; reflexes retained. | 48 hours. | No blood-clot at base. Lungs normal. Cloudy swelling of kidneys.<br>*Microscopical.*—A few active-looking pars intermedia cells remain; the cells are large and swollen; many acini filled with colloid. No anterior-lobe cells seen. |
| *Observation 44.*—Jan. 19, 1909. Old dog; dura adherent and friable; hæmorrhage; gland removed in fragments; no injury to temporal lobe. | January 20.<br>January 21.<br>January 22. | 38.4<br>36.0<br>32.0 | 142<br>90<br>80 | 140<br>80<br>60 | ..... | Lethargic; arching of back; subnormal temperature gradually became comatose; no convulsions. | 3 days. | Subcutaneous infection of wound. Brain and dura appear normal; large blood-clot at base; no evidence of remaining hypophysis. Lungs and abdominal organs normal.<br>*Microscopical.*—Organizing blood-clot at base; no pars intermedia or anterior-lobe cells found (serial sections). |
| *Observation 51.*—Feb. 24, 1909. Old dog; dura adherent and friable; small vessel at base torn while elevating temporal lobe; gland removed in fragments. | January 25. | 32.0 | 92, irregular. | 60 | ..... | Animal never entirely recovered from anæsthetic; arching of back; comatose 24 hours after the operation; subnormal temperature; weak, irregular pulse; reflexes retained; death during night. | 36 hours. | Brain and meninges appear normal; small blood-clot around stump of infundibulum.<br>*Microscopical.*—A few pars intermedia cells, infiltrated with blood. No anterior cells seen (serial sections). |
| *Observation 52.*—Feb. 25, 1909. Dry, clean operation; entire gland removed in one piece; no injury to temporal lobe. | Jan. 26 (9 a. m.)<br>(6 p. m.) | 38.6<br>36.9 | 208<br>Not palpable; heart-rate 45 to minute; feeble and irregular. | Anuria. | ..... | Onset of typical symptoms on day after operation with coma and death during the night. | 36 hours. | Brain and meninges normal; base clean; lungs and abdominal organs appear normal.<br>*Microscopical.*—The anterior and posterior lobes have been completely removed; a thin layer of pars intermedia cells remain at base, not active-looking (serial sections). Fig. 20. Thyroid cells columnar; small amount of colloid in acini; a few large swollen cells lying free in acini. |

TABLE II.—ADULT TOTAL HYPOPHYSECTOMIES.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation* 53.—March 1, 1909. Old dog; dura adherent and friable; gland removed in fragments; hemorrhage; injury to 3d nerve. | March 2 (9 a. m.)<br>(2 p. m.) | 37.5° C.<br>30.0 | 200<br>Not palpable. | 120 cc. | ..... | Had entirely recovered from the anæsthetic within 2 hours, walked around the room; drank milk and water; gradually became lethargic; was comatose 18 hours after operation. | 24 hours. | Brain and meninges appear normal; large blood-clot at base. Lungs normal; cloudy swelling of kidneys. *Microscopical.*—A few pars intermedia cells, surrounded with blood-clot. No anterior-lobe cells seen (serial sections). |
| *Observation* 57.—March 10, 1909. Dry, clean operation; good view of gland which was removed in one piece. | March 11.<br>March 12.<br>March 13.<br>March 14. | 37.5<br>37.4<br>37.7<br>30.2 | 100<br>160<br>150<br>Not palpable. | 320<br>50<br>70<br>Anuria. | Reduces Fehling's. | Promptly recovered from anæsthetic; took food and water for the first 2 days; arching of back; sugar in urine; became comatose on afternoon of 3d day; general muscular tremors; reflexes retained. | 4 days. | Brain and meninges normal; a small blood-clot at base; no evident fragments of the gland remain. Other organs appear normal. *Microscopical.*—No anterior lobe cells seen in examination of serial sections of base; a few pars intermedia cells remain. No striking change in other organs. |
| *Observation* 63.—March 18, 1909. Male; dry, clean operation; good view of gland, which was removed "in toto"; Fig. 18. | March 19.<br>March 20.<br>March 21.<br>March 22. | 37.6<br>36.2<br>36.5<br>24.0 | 90<br>120<br>60<br>Not palpable. | 160<br>120<br>40<br>Anuria. | ..... | For 2 days following operation animal was lethargic; arching of back; subnormal temperature; gradually became comatose; rectal temperature registered 14.8° C. below normal; reflexes retained. | 4 days. | No blood-clot at base; no evident remains of the gland. Lungs normal; thyroid much larger than normal; other organs appear normal. *Microscopical.*—A few pors intermedia cells remain at base; not active-looking; no anterior-lobe cells seen (serial sections). (Fig. 19.) Liver-cells vacuolated and shrunken around central vein, stain poorly. Thyroid-cells columnar; thrown up in folds; small amount of colloid in acini. |
| *Observation* 67.—March 31, 1909. Dry, clean operation; the entire gland was removed in one piece. | April 1.<br>April 2. | 38.0<br>30.2 | 160<br>120 | 70<br>Anuria. | Reduces Fehling's. | Recovered from anæsthetic with usual promptness; lethargy; arching of back; general muscular tremors; subnormal temperature; coma and death. | 48 hours. | Brain and meninges normal. Thyroid slightly larger than usual; parathyroid large and prominent. Lungs normal. Liver, kidneys and pancreas appear normal. *Microscopical.*—The anterior and posterior lobes have been completely removed. A few pars intermedia cells remain at base; not active-looking. Thyroid-cells columnar; many newly formed acini. Liver and pancreas and adrenal appear normal. |
| *Observation* 76.—May 5, 1909. Dry, clean operation; entire gland removed in one piece. | May 6 (9 a. m.)<br>(4 p. m.) | 36.2<br>22.0 | 60<br>Not palpable. | Anuria. | ..... | Recovered from anæsthetic; soon became very dull; refused food; temperature subnormal; respirations slow and deep (7 to minute); gradually became comatose. | 48 hours. | Wound clean; no evidence of any remaining hypophyseal tissue. Other organs appear normal. *Microscopical.*—A few pars intermedia cells at base; infiltrated with blood; not active-looking; no anterior-lobe cells seen (serial sections). Thyroid, normal; liver, diffuse vacuolation of the cells; nuclei stain well. |

TABLE III.—PUPPY TOTAL HYPOPHYSECTOMIES.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation* 58.—March 10, 1909. Dry, clean operation; the entire gland removed in one piece. | March 11.<br>March 14.<br>March 16.<br>March 20.<br>March 25.<br>March 28.<br>March 29.<br>March 30. | 38.8° C.<br>38.8<br>38.5<br>38.8<br>39.2<br>38.4<br>38.6<br>39.2 | 240<br>180<br>130<br>160<br>196<br>140<br>120<br>96, weak and irregular. | 320 cc.<br>500<br>900<br>1000<br>500<br>320<br>380<br>40 | 8¼ lbs.<br><br><br>10 lbs.<br>10½ lbs.<br><br><br>10½ lbs. | On day following operation animal bright and playful as before; with the exception of a transient polyuria, the puppy remained apparently normal for 19 days; gained 2¼ lbs. in weight; sudden onset of symptoms of cachexia hypophyseopriva; lethargy; subnormal temperature; arching of back; gradually became comatose. | 20 days. | Base of brain clean; no evident remains of the hypophysis. Liver, large and friable, dark red in color with numerous opaque areas of necrosis. Other organs seem normal. *Microscopical.*—A few pars intermedia cells remain; no anterior lobe (serial sections). Thyroid-cells cuboidal in shape; greatly swollen; small amount of colloid in acini. Liver-necrosis, usually limited to the center of the lobule. Cloudy swelling of kidneys. |

TABLE III.—PUPPY TOTAL HYPOPHYSECTOMIES.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 59.*—March 12, 1909. Dry, clean operation; no bleeding; gland removed "in toto." | March 13.<br>March 14.<br>March 15. | 37.7° C.<br>35.5<br>29.0 | 160<br>136<br>Not palpable; heart-rate 60 to minute. | 300 cc.<br>160<br>Anuria. | 6½ lbs. | Animal promptly recovered from anæsthetic, and for 24 hours was bright and playful; appetite good; on the morning of the 2d day began to grow lethargic; subnormal temperature; arching of back; refused food; comatose on 3d day; rectal temperature 29° C. (temperature of the room 24° C.); blood pressure low. | 3 days. | Complete removal of hypophysis; base clean; no blood-clot; no injury to temporal lobe. Thyroid, lungs, liver, kidney, adrenal, and pancreas all appear normal.<br>*Microscopical.*—No anterior-lobe cells (serial sections); thyroid normal; other organs appear normal. |
| *Observation 60.*—March 12, 1909. Entire gland removed in one piece; no operative complications. | March 13.<br>March 14.<br>March 15.<br>March 17.<br>March 19.<br>March 21.<br>March 23.<br>March 25.<br>March 28.<br>March 29. | 38.8<br>38.8<br>38.4<br>37.2<br>36.8<br>36.2<br>34.0<br>33.0<br>26.0<br>22.0 | 162<br>140<br>140<br>80<br>76<br>80<br>80<br>82<br>Not palpable.<br>Not palpable. | 990<br>620<br>340<br>180<br>220<br>85<br>60<br>90<br><br>Anuria. | 12½ lbs.<br><br><br><br><br><br><br><br><br>10¼ lbs. | Transient polyuria; otherwise normal for 3 days following operation; began to grow stupid on 4th day; gradual fall of temperature; arching of back; poor appetite; general muscular tremors; became comatose on 14th day; death on 15th day; temperature 22° C.; no convulsions; cf. Figs. 12 and 13. | 15 days. | No evident remains of hypophysis; no blood-clot at base; no injury to temporal lobe. Thyroid appears normal; also lungs, liver, pancreas, adrenal and kidneys.<br>*Microscopical.*—No anterior-lobe cells (serial sections, Fig. 21); a few pars intermedia cells; not active-looking. Other organs normal. |
| *Observation 62.*—March 18, 1909. Entire gland removed in one piece; no operative complications. | March 19.<br>March 20.<br>March 21.<br>March 22.<br>March 23. | 38.6<br>38.4<br>38.2<br>28.0<br>20.0 | 182<br>165<br>142<br>Not palpable.<br>Not palpable. | 1500<br>800<br>500<br>60<br>Anuria. | 10½ lbs. | Animal bright and playful for 3 days following the operation; sudden onset of symptoms of cachexia hypophyseopriva. | 5 days. | Base clean; no remains of hypophysis to be seen. Lungs normal. Thyroid normal; liver, pancreas, adrenals and kidneys appear normal.<br>*Microscopical.*—No anterior-lobe cells (serial sections); a few pars intermedia cells; other organs appear normal. |
| *Observation 64.*—March 22, 1909. Entire gland removed in one piece; no operative complications. | March 23.<br>March 25.<br>March 27.<br>March 28.<br>March 30.<br>April 1.<br>April 3.<br>April 5. | 38.6<br>38.5<br>38.2<br>37.2<br>37.7<br>38.0<br>37.8<br>30.0 | 152<br>160<br>180<br>108<br>80<br>160<br>60<br>60 | 1100<br>520<br>380<br>100<br>240<br>260<br>200<br>40 | 9½ lbs.<br><br><br><br><br><br><br>9¼ lbs. | Bright and playful (Fig. 14) until 24 hours before death; transient polyuria; slightly subnormal temperature for 10 days; sudden onset with coma; fall in temperature; irregular, feeble pulse. | 14 days. | Base clean; no evident remains of hypophysis. Lungs, thyroid, liver, adrenals, pancreas and kidneys appear normal.<br>*Microscopical.*—No anterior-lobe cells (serial sections). A few pars intermedia cells. Thyroid normal; also the other organs. |
| *Observation 65.*—March 27, 1909. Entire gland removed in one piece; no operative complications. | March 28.<br>March 29.<br>March 30.<br>April 1.<br>April 3.<br>April 4.<br>April 5. | 38.6<br>38.0<br>40.0<br>38.9<br>38.6<br>38.4<br>29.0 | 160<br>142<br>156<br>120<br>96<br>80<br>Not palpable. | 200<br>900<br>640<br>280<br>145<br>200<br>..... | 9 lbs.<br><br><br><br><br><br>9½ lbs. | Bright and playful until 24 hours before death; transient polyuria; sudden onset of symptoms of cachexia hypophyseopriva on 8th day. | 9 days. | Base clean; no evident remains of hypophysis. Thyroid, lungs, thymus, liver, kidneys, pancreas and adrenals all appear normal.<br>*Microscopical.*—No anterior-lobe cells (serial sections). The usual amount of pars intermedia remains; not active-looking. Diffuse vacuolation of the liver-cells. |
| *Observation 70.*—April 7, 1909. Entire gland removed in one piece; no operative complications. | April 8.<br>April 9.<br>April 12.<br>April 15.<br>April 18.<br>April 20.<br>April 22.<br>April 23. | 38.8<br>38.6<br>38.7<br>38.0<br>38.2<br>38.8<br>38.6<br>26.0 | 154<br>160<br>147<br>100<br>92<br>120<br>86<br>36 | 600<br>740<br>500<br>200<br>230<br>160<br>140<br>..... | 8 lbs.<br><br>7¼ lbs.<br><br><br><br><br>7½ lbs. | Bright and playful until 24 hours before death; transient polyuria; sudden onset of symptoms of cachexia hypophyseopriva; gradually became comatose; arching of back; slow, irregular pulse; subnormal temperature; irregular jerking contractions of the depressors of the jaw, and extensors of the fore-legs. | 16 days. | Base clean; no blood-clot; no remains of hypophysis. Thyroid looks normal. Thymus and anterior mediastinum œdematous; fatty degeneration of the liver; adrenals and pancreas appear normal; cloudy swelling of kidneys.<br>*Microscopical.*—No anterior-lobe cells (serial sections). A few pars intermedia cells remain at base; many acini distended with colloid-like material; cells swollen. Thymus œdematous and congested with blood; liver fatty; other organs appear normal. |
| *Observation 89.*—May 28, 1909. Entire gland removed in one piece; no operative complications. | May 29.<br>May 30.<br>May 31.<br>June 1.<br>June 2.<br>June 3.<br>June 4 (8 a. m.)<br>(4 p. m.) | 38.6<br>38.6<br>38.5<br>38.5<br>38.8<br>38.2<br>36.0<br>33.2 | 180<br>136<br>100<br>100<br>120<br>80<br>60<br>Not palpable. (Fig. 16). | 500<br>280<br>160<br>120<br>130<br>90<br>80<br>Anuria. | 12 lbs.<br><br><br><br><br><br><br>11¼ lbs. | Bright and playful (cf. Fig. 15), until onset of symptoms of cachexia hypophyseopriva on 6th day. | 7 days. | Base clean; no evident remains of hypophysis. Thyroid, lungs, thymus, adrenals, pancreas and kidneys appear normal; surface of liver contains a few small opaque areas of necrosis.<br>*Microscopical.*—No anterior-lobe cells (serial sections); a few active-looking pars intermedia cells; colloid bodies seem to be passing into 3d ventricle. Thyroid normal; necrosis around central vein in liver; other organs appear normal. |

TABLE IV.—REMOVALS OF POSTERIOR LOBE ALONE.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation* 25.—Dec. 4, 1908. Adult bull terrier; male; (Fig. 25); dry, clean operation; removal of posterior lobe and the greater portion of the pars intermedia; no operative complications. | December 5. | 38.6° C. | 150 | 200 cc. | 18½ lbs. | Promptly recovered from operation; remained normal; appetite good; had 2 attacks with general convulsions, salivation and unconsciousness; so erotic that could not be kept in the yard with other animals; sacrificed for the purpose of histological study. | Sacrificed 6 months after operation. | Anterior lobe looks normal; posterior lobe absent. Thyroid, large and firm; other organs appear normal. *Microscopical.*—Posterior lobe removed; many large "colloid bodies" in stalk and in the brain substance around 3d ventricle; anterior lobe appears normal in arrangement and staining; contains a large cyst filled with a faintly bluish staining colloid. Thyroid cells flat; acini distended with colloid; other organs normal. Testicle, active spermatogenesis. |
| | December 15. | 38.6 | 144 | 280 | | | | |
| | December 30. | 38.8 | 140 | 350 | | | | |
| | January 30. | 38.6 | 120 | 320 | 20 lbs. | | | |
| | February 20. | 38.2 | 90 | 430 | 20 lbs. | | | |
| | March 30. | 38.6 | 80 | 360 | 20 lbs. | | | |
| | April 30. | 38.4 | 69 | 380 | 18¾ lbs. | | | |
| | May 30. | 38.4 | 72 | 280 | 19½ lbs. | | | |
| *Observation* 85.—May 19, 1909. Puppy; Fig. 23; uncomplicated posterior lobe removal. | May 20. | 38.8 | 140 | 800 | 10 lbs. | Promptly recovered from operation; transient polyuria; otherwise perfectly normal in every particular for 22 days; bright and playful. On the morning of 23d day animal looked sick; refused food; gradually became comatose; death at 4 p. m.; no convulsions. | 23 days. | Well nourished; brain and meninges appear normal; anterior lobe looks normal; posterior lobe removed. Thyroids larger than normal; lungs, adrenals, testicles and kidneys appear normal. *Microscopical.*—Anterior lobe normal in appearance. Liver shows extreme degeneration. Other organs normal. |
| | May 21. | 38.8 | 100 | 800 | | | | |
| | May 22. | 38.2 | 144 | 420 | | | | |
| | May 25. | 38.5 | 140 | 300 | | | | |
| | May 30. | 38.8 | 152 | 315 | | | | |
| | June 5. | 38.6 | 136 | 260 | | | | |
| | June 10. | 38.8 | 115 | 280 | | | | |
| | June 11. | 36.2 | 120 | 320 | 11¼ lbs. | | | |
| *Observation* 86.—May 20, 1909. Puppy; Fig. 24; uncomplicated posterior lobe removal. | May 21. | 38.0 | 120 | 580 | 10½ lbs. | Transient polyuria; gain in weight; remained bright and playful; no convulsions; sacrificed 50 days after the operation. | Sacrificed 50 days after operation. | Animal well nourished; anterior lobe appears normal; thyroids and other organs appear normal. *Microscopical.*—Anterior lobe partly destroyed by scar-tissue the greater portion, however, is normal in appearance. Liver, diffuse vacuolization of cells but most marked in center of lobules. |
| | May 23. | 38.2 | 136 | 860 | | | | |
| | May 25. | 38.6 | 132 | 480 | | | | |
| | May 27. | 38.2 | 120 | 185 | | | | |
| | May 28. | 37.2 | 60 | 160 | | | | |
| | May 29. | 39.4 | 90 | 180 | 12 lbs. | | | |
| | June 1. | 38.2 | 86 | 300 | | | | |
| | June 5. | 38.4 | 82 | 240 | | | | |
| | June 15. | 38.6 | 76 | 280 | | | | |
| | June 25. | 38.5 | 68 | 300 | | | | |
| | June 30. | 38.3 | 92 | 140 | 13½ lbs. | | | |

TABLE V.—TOTAL REMOVAL OF ANTERIOR LOBE ALONE.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation* 7.—Oct. 8, 1908. Fox terrier; adult; complete removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications. | October 9. | 39.2° C. | 140 | 420 cc. | ..... | Promptly recovered from the anæsthetic; was bright and lively on the day following the operation; symptoms of cachexia hypophyseopriva appeared 48 hours after the operation; animal gradually became comatose; temperature subnormal; pulse slow and irregular; death on third day. | 68 hours. | Wound healing per primam. Posterior lobe found in sella turcica; blood-supply intact; surrounded with blood-clot. Other organs appear normal. *Microscopical.*—No anterior-lobe cells found in serial sections of the base; posterior lobe and pars intermedia stain normally. The interstices of the posterior lobe are filled with numerous small "colloid bodies" (Fig. 30), converging at the stalk, and passing upward into third ventricle. Other organs normal. |
| | October 10. | 37.2 | 116 | 80 | | | | |
| | October 11. | 32.0 | 60, irregular. | 60 | | | | |
| *Observation* 9.—Oct. 13, 1908. Bull terrier; adult; total removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications. | October 14. | 39.2 | 165 | 140 | ..... | Never entirely recovered consciousness; arching of back; subnormal temperature; feeble, irregular pulse. | 48 hours. | Wound healing per primam. Posterior lobe found in sella turcica; blood-supply intact; surrounded with blood-clot. Other organs appear normal. *Microscopical.*—Floor of 3d ventricle torn out; no anterior-lobe cells found in serial sections. Posterior lobe lost in sectioning. Other organs normal. |
| | October 15. | 34.0 | 52 | 45 | | | | |
| *Observation* 23.—Dec. 1, 1908. Fox terrier; adult; total removal of anterior lobe; posterior lobe left in place; dry, clean operation; no operative complications. | December 2. | 38.4 | 200, irregular. | 85 | ..... | The symptoms of cachexia hypophyseopriva were well marked on the day following the operation; animal gradually became comatose. | 48 hours. | Wound healing per primam. Blood-clot at base; posterior lobe found in place, appears normal. Other organs appear normal. *Microscopical.*—Specimen removed at operation shows entire anterior lobe and floor of 3d ventricle. Base, no anterior-lobe cells seen. Posterior lobe stains normally; contains many "colloid bodies." |
| | December 3. | 29.0 | Not palpable. | Anuria. | | | | |

TABLE VI.—STALK SEPARATIONS.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 29.*—Nov. 25, 1908. Puppy; dry, clean operation; gland separated from base; no operative complications. | November 26. | 38.2° C. | 192 | 2000 cc. | ..... | With the exception of a marked polyuria the animal was apparently normal in every particular for a week following the operation. Sudden onset of usual symptoms of cachexia hypophyseopriva; death at 10 a. m. on December 5. | 10 days. | No evidence of infection. Hypophysis adherent to base in normal situation—brilliant red color—no gross changes in other organs. *Microscopical*—Both lobes entirely degenerated and largely replaced by fibroblasts, etc. Patches of normal pars intermedia still apparent. One microscopic clump of stainable anterior-lobe cells at anterior angle. Thyroid and parathyroid show slight hyperplasia; other organs normal. |
| | November 27. | 38.6 | 160 | 2260 | | | | |
| | November 30. | 38.6 | 142 | 1600 | | | | |
| | December 1. | 40.0 | 156 | 1200 | | | | |
| | December 2. | 38.0 | 92 | 800 | | | | |
| | December 3. | 28.6 | 51 | 60 | | | | |
| | December 4. | 22.0 | Not palpable. | Anuria. | | | | |
| *Observation 33.*—Dec. 18, 1908. Fox terrier; adult; same operation. | December 19. | 37.2 | 156 | 880 | 14 lbs. | For 10 days following the operation animal was lethargic; temperature slightly subnormal; arching of back; appetite poor, and was rapidly becoming cachectic; was given daily subcutaneous injections—10 cc. of a 1 per cent aqueous extract of anterior lobe of ox—for one month; marked improvement; gained in weight; temperature remained normal and appetite good; was sacrificed on May 10 for the purpose of making histological study of the tissues. | Sacrificed 5 months after the operation. | The hypophysis has become reattached to the base; appears flattened and shrunken. Testicles appear much smaller than normal; other organs seem normal. *Microscopical.*—The hypophysis is surrounded by scar-tissue, and is firmly adherent to the floor of the third ventricle; a thin layer of scar-tissue marks the line of recent division of the stalk (cf. Fig. 28). Anterior lobe contains a large colloid cyst; cells small and brightly stained with eosin. Posterior lobe invaded by down-growths of pars intermedia; many acini filled with colloid. Testicles, many of tubules lined with a single layer of cells; there is a marked increase in the "zwischen-zellen." Other organs normal. |
| | December 20. | 38.0 | 132 | 935 | | | | |
| | December 22. | 37.8 | 116 | 950 | | | | |
| | December 24. | 38.2 | 94 | 620 | | | | |
| | January 1. | 37.4 | 82 | 465 | 12 lbs. | | | |
| | January 1 to February 5.—Daily injections (subcutaneous) of a 1 per cent anterior lobe extract; daily amount of urine varied from 240 to 600 cc.; no sugar. | | | | | | | |
| | February 25. | 38.5 | 136 | ..... | 14 lbs. | | | |
| | March 29. | 38.8 | 116 | 380 | 16 lbs. | | | |
| | April 25. | 38.5 | 100 | 320 | 17½ lbs. | | | |
| | May 10. | 38.8 | 136 | 260 | 18 lbs. | | | |
| *Observation 35.*—Dec. 18, 1908. Fox terrier; adult; same operation. | December 19. | 38.6 | 212 | 1400 | ..... | Transient polyuria; gradual onset of symptoms of cachexia hypophyseopriva, becoming comatose on the 23d day; anuria; diarrhœa; weak, irregular pulse; subnormal temperature (21° C.). | 24 days. | The gland has become reattached to the base; surrounded by scar-tissue. Lungs and other organs appear normal. *Microscopical.*—A thin line of scar-tissue marks the site of the recent division of the stalk. Posterior lobe appears normal; a few anterior-lobe cells stain brightly with eosin; pars intermedia cells appear normal. Testicles not examined; other organs normal. |
| | December 21. | 38.5 | 132 | 900 | | | | |
| | December 26. | 38.2 | 140 | 640 | | | | |
| | December 29. | 38.8 | 135 | 400 | | | | |
| | January 2. | 37.2 | 96 | 140 | | | | |
| | January 5. | 36.8 | 80 | 80 | | | | |
| | January 8. | 36.4 | 72 | 45 | | | | |
| | January 10. | 35.0 | 52 | Anuria. | | | | |
| | January 11. | 21.0 | Not palpable. | Anuria. | | | | |
| *Observation 83.*—May 12, 1909. Bull terrier; adult; same operation. | May 14. | 38.4 | 136 | 700 | ..... | Transient polyuria; had purulent discharge from both nostrils; sacrificed on June 10; (Fig. 26). | Sacrificed 28 days after the operation. | Wounds healed per primam. Frontal sinus full of pus; areas of bronchial pneumonia in both lungs. Thyroids large and firm. Testicles appear normal. Hypophysis reattached to base; surrounded by scar-tissue. *Microscopical.*—Serial sections of the base of the brain and hypophysis show the separation to have been complete; has become reattached by scar-tissue. Posterior lobe contains many acini of pars intermedia cells filled with colloid; anterior lobe appears normal. Thyroid, large acini filled with colloid, cells flat. Testicles and other organs appear normal. |
| | May 19. | 38.9 | 84 | 430 | | | | |
| | May 21. | 38.5 | 100 | 500 | | | | |
| | May 26. | 38.4 | 72 | 400 | | | | |
| | June 1. | 38.4 | 64 | 200 | | | | |
| | June 5. | 38.6 | 72 | 320 | | | | |
| | June 8. | 37.2 | 52 | 280 | | | | |
| | June 10. | 36.0 | 60 | 180 | | | | |

TABLE VI.—STALK SEPARATIONS.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 90.*—May 29, 1909. Puppy; same operation. | May 30.<br>May 31.<br>June 2.<br>June 4.<br>June 7.<br>June 9. | 38.8° C.<br>38.6<br>39.2<br>38.8<br>38.6<br>38.8 | 180<br>160<br>80<br>100<br>92<br>86 | 260 cc.<br>300<br>240<br>250<br>180<br>165 | ..... | Promptly recovered from operation, and remained bright and playful; temperature and pulse normal; urine approximately normal; was sacrificed in order to make an histological study of the tissues. | Sacrificed on 12th day after the operation. | Wounds healed per primam. Hypophysis firmly adherent to base, but to the left of its normal situation; surrounded by organizing blood-clot. Thyroids, lungs, liver, adrenal, pancreas, kidneys and ovaries appear normal.<br>*Microscopical.*—Portion of anterior lobe replaced by fibroblasts; the cells of the remaining fragment are large and faintly staining, very few eosinophiles. Posterior lobe very cellular, contains excess of thin colloid and hyaline bodies (cf. Fig. 30). Other organs appear normal. |

TABLE VII.—PARTIAL REMOVAL OF PARS ANTERIOR LEAVING POSTERIOR LOBE.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 26.*—Dec. 4, 1908. Adult cur; partial hypophysectomy; poor exposure; bleeding; about $\frac{2}{3}$ of anterior lobe removed; posterior lobe left in place; injury to temporal lobe. | December 5.<br>December 6.<br>December 7.<br>December 8.<br>December 9.<br>December 10. | 39.0° C.<br>38.6<br>38.8<br>38.2<br>36.0<br>27.6 | 192<br>88<br>112<br>160<br>90<br>Not palpable. | 1200 cc.<br>860<br>400<br>150<br>25<br>Anuria. | ..... | Rotary progression; transient polyuria; onset of symptoms of cachexia hypophyseopriva on 5th day; transfusion of blood on 6th day; no improvement; death at 6 p. m. | 6 days. | Small blood-clot at base surrounding the posterior lobe and a fragment of anterior lobe. Other organs appear normal.<br>*Microscopical.*—Posterior lobe in place with stalk and blood-supply intact; surrounded by active-looking pars intermedia cells; large number of "colloid bodies" in body of posterior lobe and in the brain substance surrounding the 3d ventricle. A few normal-looking anterior-lobe cells seen (serial sections). |
| *Observation 27.*—Dec. 4, 1908. Adult hound; male; partial hypophysectomy; the greater part of the anterior lobe was removed; no operative complications. | December 5.<br>December 10.<br>December 30.<br>January 17.<br>February 25.<br>March 29.<br>April 14.<br>May 5. | 38.2<br>38.3<br>37.6<br>38.0<br>38.5<br>38.0<br>38.2<br>38.4 | 152<br>132<br>140<br>100<br>100<br>60<br>72<br>80 | 2000<br>1450<br>1200<br>750<br>645<br>680<br>450<br>320 | 18 lbs.<br>19 lbs.<br>21 lbs.<br>22½ lbs.<br>24 lbs.<br>25 lbs.<br>24 lbs. | Transient polyuria; gain in weight (18 to 24 lbs.); loss of hair; impotence; appetite remained good; entire right thyroid removed on December 15; left thyroid removed on April 30; dull and stupid for several days; refused food; death on May 5; no definite attacks of tetany. | 5 months. | Well nourished; hair thin; skin thick and oedematous; brain and meninges appear normal; no evident remains of anterior lobe; posterior lobe in place. No thyroid or parathyroid tissue could be found. Ovaries small, buried in fat.<br>*Microscopical.*—A few active-looking anterior-lobe cells (serial sections); posterior lobe contains many "colloid bodies"; proliferation of pars intermedia. Ovaries small. Contain very few developing follicles. Cloudy swelling of kidneys; other organs normal. |
| *Observation 29.*—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of anterior lobe; posterior lobe left in place; no operative complications; pneumonia. | December 12.<br>December 15.<br>December 25.<br>January 1.<br>January 15. | 38.2<br>38.2<br>38.0<br>38.8<br>39.8 | 180<br>124<br>120<br>140<br>200 | 650<br>490<br>300<br>240<br>120 | 20 lbs.<br>20½ lbs. | Transient polyuria; no striking gain in weight; apparently normal till January 10; developed a purulent discharge from nose, cough, rapid respiration, etc.; death on January 18. | Death from pneumonia on 38th day. | Wound healed per primam. Lungs consolidated; brain and meninges appear normal; no evidence of anterior lobe; posterior lobe in place.<br>*Microscopical.*—A few active anterior-lobe cells (serial sections). Posterior lobe attached to base by stalk; contains many "colloid bodies." Lungs consolidated; other organs not examined. |
| *Observation 30.*—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of anterior lobe; posterior lobe left in place; no operative complications. | December 12.<br>December 15.<br>December 30.<br>January 5.<br>January 20.<br>January 24.<br>January 25. | 38.6<br>38.8<br>38.4<br>38.6<br>38.0<br>32.0<br>26.0 | 118<br>128<br>72<br>84<br>60<br>42<br>Not palpable. | 800<br>130<br>120<br>160<br>180<br>40<br>Anuria. | 14 lbs.<br>14 lbs. | Promptly recovered from operation; transient polyuria; no gain in weight; sudden onset of symptoms of cachexia hypophyseopriva; temperature fell to 26° C.; arching of back; coma; death at 10 a. m. | 45 days. | Brain and meninges appear normal; posterior lobe in place; no evidence of anterior lobe. Other organs appear normal.<br>*Microscopical.*—By a careful search through serial sections of the base a few anterior-lobe cells are found imbedded in scar-tissue. Posterior lobe being invaded by fibroblasts. The specimen removed at operation shows what is apparently the entire anterior lobe. Other organs normal. |

TABLE VII.—PARTIAL REMOVAL OF PARS ANTERIOR LEAVING POSTERIOR LOBE.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 31.*—Dec. 11, 1908. Fox terrier; adult; partial hypophysectomy; an apparently complete removal of the anterior lobe; posterior lobe left in place; no operative complications. | December 12.<br>December 15.<br>December 18.<br>December 21.<br>December 30.<br>January 1.<br>January 4.<br>January 5.<br>January 6. | 38.6° C.<br>38.2<br>38.4<br>37.8<br>38.2<br>38.0<br>37.4<br>35.0<br>27.0 | 120<br>126<br>90<br>98<br>80<br>72<br>84<br>56<br>Not palpable. | 800 cc.<br>620<br>170<br>210<br>100<br>80<br>100<br>40<br>Anuria. | 17½ lbs.<br><br><br><br>18 lbs. | Transient polyuria; gradual onset of symptoms of cachexia hypophyseopriva; lethargy; subnormal temperature; arching of back; diminished output of urine; coma; death on January 6. | 26 days. | Posterior lobe in place; no evidence of anterior lobe; thyroid slightly larger than normal; other organs seem normal.<br>*Microscopical.*—A few anterior-lobe cells surrounded with scar-tissue (serial sections). Finger-like processes of pars intermedia projecting into posterior lobe; many acini filled with colloid; many "colloid bodies" in posterior lobe and stalk. Cells of thyroid are columnar; very little colloid; other organs normal. |
| *Observation 35.*—Dec. 18, 1908. Fox terrier; adult; stalk separation and partial hypophysectomy; only a very small portion (about one-third) of anterior lobe was removed; posterior lobe left in place; no operative complications. | December 19.<br>December 30.<br>January 20.<br>February 25.<br>March 4.<br>March 31.<br>April 15.<br>May 10.<br>May 30.<br>June 12.<br>June 14.<br><br>June 15.<br>June 16.<br>June 17. | 38.2<br>38.0<br>38.4<br>37.6<br>38.2<br>37.4<br>38.1<br>38.6<br>37.0<br>38.2<br>38.6<br><br>40.8<br>40.0<br>39.8 | 145<br>128<br>100<br>92<br>86<br>76<br>84<br>98<br>120<br>105<br>136, injection of anterior lobe.<br><br>120<br>98<br>120 | 1200<br>1520<br>980<br>865<br>675<br>820<br>940<br>1440<br>1000<br>1140<br>880<br><br>940<br>2400<br>1920 | 14 lbs.<br><br>17½ lbs.<br>19½ lbs.<br>19½ lbs.<br>22 lbs.<br>22 lbs.<br>23 lbs.<br>23¾ lbs.<br>24 lbs.<br><br><br><br><br> | Polyuria for six months (675 to 2400 cc. per diem); gain in weight (14 to 24 lbs.); dull; moves slowly and deliberately; not in "heat" for six months; reaction to subcutaneous injection of 3 cc. of a 1 per cent solution of anterior lobe of pig; rise in temperature from 38.6 to 40.8° C.; animal quite sick; polyuria (2400 cc. for 24 hours); animal sacrificed on June 17. | Sacrificed at end of 6 months. | Animal very fat. Brain and meninges look normal; hypophysis slightly smaller than normal; firmly adherent to floor of 3d ventricle. Thyroids are about normal in size; lungs normal; fatty degeneration of heart muscle; liver is greyish-white in color (fatty degeneration); fatty degeneration of kidneys; other organs appear normal.<br>*Microscopical.*—About two-thirds of the anterior lobe remains at base; vessels, prominent, running between strands of eosinophilic cells (smaller than normal); many collections of nuclei, without protoplasm. Posterior lobe invaded by finger-like processes of pars intermedia cells; many of the acini contain colloid-like material. Fatty degeneration of myocardium, liver and kidneys. Pancreas appears normal. Ovary contains many developing ovules, and the remnants of three lutean cysts. |

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 43.*—Jan. 14, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base. | January 15.<br>January 16. | 36.2° C.<br>25.8 | 60<br>Not palpable. | 150 cc. | ..... | Never entirely recovered from anæsthetic; subnormal temperature and slow irregular pulse, which finally became so feeble that it could not be palpated; death at 11 a. m. | 1½ days. | Wound clean; large blood-clot at base; a small fragment of anterior lobe remains attached to base. Other organs appear normal.<br>*Microscopical.*—Serial sections of the base show a few anterior-lobe cells infiltrated with blood (not active). Cloudy swelling of kidneys; other organs normal. |
| *Observation 49.*—Feb. 23, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base. | February 24.<br>February 25.<br>February 26.<br>March 1.<br>March 5.<br>March 8.<br>March 11.<br>March 13. | 36.6<br>36.6<br>37.8<br>38.6<br>38.8<br>38.0<br>38.6<br>38.4 | 140<br>180<br>120<br>92<br>115<br>100<br>120<br>136 | 120<br>60<br>145<br>160<br>200<br>120<br>165<br>190 | ..... | Symptoms of cachexia hypophyseopriva for three days following the operation; gradually recovered and was sacrificed on 21st day following operation. | Sacrificed 21 days after the operation. | Organizing blood-clot at base; no recognizable hypophyseal remains. Thyroid large and soft; other organs appear normal.<br>*Microscopical.*—Serial sections of base show a small island of active-looking anterior-lobe cells surrounded with scar-tissue; the cells are large, finely granular, with vesicular nuclei. Thyroid cells columnar; acini contain but very little colloid. Other organs normal. |

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 54.*—March 1, 1909. Spaniel; adult; male; (Fig. 39); partial hypophysectomy; a small fragment of anterior lobe was left; no operative complications. | March 2.<br>March 3.<br>March 5.<br>March 30.<br>April 20.<br>May 20.<br>June 15. | 38.5° C.<br>39.3<br>38.2<br>38.6<br>38.6<br>38.8<br>37.6 | 130<br>128<br>110<br>128<br>136<br>140<br>132 | 500 cc.<br>1600<br>950<br>1200<br>860<br>900<br>780 | 16 lbs.<br><br><br>18 lbs.<br>25¾ lbs.<br>27 lbs.<br>27 lbs. | Transient glycosuria; polyuria (500 to 1600 cc.) continued for 3½ months; gain in weight (from 16 to 27 lbs.); for a week following the operation animal was dull, sleeping heavily most of the time; began to improve, and for the remaining three months was very lively and playful; intravenous injection of 3 cc. of 1 per cent aqueous extract of anterior lobe (pig) caused a marked rise in blood pressure and body temperature. | Sacrificed 3½ months after the operation. | Animal very fat. Brain and meninges appear normal; no recognizable remains of the hypophysis. Thyroids appear normal; fatty degeneration of liver; pancreas, adrenals, ovaries and kidneys appear normal.<br>*Microscopical.*—A small area of active-looking anterior-lobe cells surrounded by scar-tissue (serial sections). Thyroid cells flat; acini distended with colloid. Other organs appear normal. |
| *Observation 55.*—March 3, 1909. Fox terrier; adult; male; (Figs. 40, 41); partial hypophysectomy; a small fragment of anterior lobe was unintentionally left. | March 4.<br>March 5.<br>March 6.<br>March 30.<br>April 30.<br>May 30.<br>June 15. | 38.5<br>39.0<br>38.5<br>38.2<br>38.4<br>38.2<br>38.4 | 165<br>120<br>76<br>88<br>88<br>72<br>92 | 1100<br>870<br>230<br>460<br>580<br>640<br>800 | 17 lbs.<br><br><br>18½ lbs.<br>21½ lbs.<br><br>23 lbs. | Polyuria (340 to 1100 cc.) for 3½ months; atrophy of testicles (cf. Fig. 40); gain in weight (17 to 23 lbs.); intravenous injection of 3 cc. of 1 per cent aqueous extract of anterior lobe (pig) caused a rise in blood pressure, marked increase in respirations, and a subsequent rise in temperature (38.4 to 42.5° C.). | Sacrificed 3½ months after the operation. | No recognizable remains of hypophysis; thyroid, liver, adrenals and kidneys appear normal. Testicles about half the normal size.<br>*Microscopical.*—A few normally-staining anterior-lobe cells surrounded with scar-tissue (serial sections); thyroid cells of normal size; acini distended with colloid. Testicles, absence of spermatogenetic cells. |
| *Observation 61.*—March 16, 1909. Puppy; (Fig. 35); partial hypophysectomy; a small fragment of anterior lobe was unintentionally left at the base. | March 17.<br>March 20.<br>March 30.<br>April 10.<br>May 10.<br>May 12.<br>May 15. | 38.5<br>38.6<br>38.8<br>38.3<br>37.3<br>36.5<br>35.8 | 184<br>142<br>160<br>128<br>112, distemper.<br>100<br>80 | 740<br>185<br>100<br>150<br>180<br>60<br>45 | 5½ lbs.<br><br>6½ lbs.<br>7½ lbs.<br><br><br> | Promptly recovered from operation; transient polyuria; was apparently normal in every particular for six weeks; gained 2 lbs. in weight; was growing rapidly; distemper; sudden appearance of symptoms of cachexia hypophyseopriva on May 10 (Fig. 35); gradually grew worse; subnormal temperature; arching of back; weak, irregular pulse, and coma. | 60 days. | Base of brain contains a thin layer of scar-tissue; no recognizable hypophyseal remains; other organs appear normal.<br>*Microscopical.*—Small group anterior-lobe cells in scar-tissue; large and active in appearance. Few active-looking pars intermedia cells. Liver cells around central vein vacuolated and stain poorly; other organs show no marked changes. |
| *Observation 66.*—March 28, 1909. Puppy; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base. | March 29.<br>March 30.<br>April 5.<br>April 10.<br>April 15.<br>April 25.<br>May 1.<br>May 3.<br>May 4. | 38.6<br>38.9<br>38.6<br>38.5<br>37.5<br>37.8<br>37.0<br>26.0<br>17.5 | 185<br>160<br>136<br>148<br>84<br>60<br>90<br>Not palpable.<br>Not palpable. | 1260<br>980<br>800<br>1240<br>420<br>200<br>105<br>Anuria.<br>Anuria. | 10½ lbs.<br><br><br>12¾ lbs.<br><br><br><br><br> | Promptly recovered from anæsthetic, and with the exception of polyuria was normal in every particular for 2 weeks following the operation; gained 2¼ lbs. in weight; gradually became lethargic; slowly falling temperature; arching of back; slow, irregular pulse; became comatose on May 3; death on May 4 at 11 a. m. | 37 days. | Brain and meninges appear normal; no remains of the hypophysis seen on gross inspection. Testicles much smaller than those of a control puppy of the same age. Liver necroses.<br>*Microscopical.*—A few anterior-lobe cells of the large-active type can be seen surrounded with dense scar-tissue (serial sections). (Fig. 36.) Thyroid normal. Liver cells vacuolated around central vein. Other organs normal. Testicles, tubules lined with single layer of cells; no spermatogenetic cells. |
| *Observation 71.*—April 12, 1909. Adult black and tan bitch; Fig. 38; partial hypophysectomy; a fragment of anterior lobe was unintentionally left. | April 13.<br>April 15.<br>April 25.<br>May 10.<br>May 30.<br>June 10. | 38.0<br>38.2<br>38.8<br>38.6<br>37.8<br>38.0 | 165<br>142<br>120<br>80<br>72<br>60 | 1100<br>1520<br>460<br>200<br>340<br>280 | ..... | Animal promptly recovered from the operation, and with the exception of a transient polyuria seemed normal in every way; sacrificed June 10. | Sacrificed 58 days following the operation. | Well nourished; wound healed per primam. Base of brain clean; no evident remains of the hypophysis. Areas of focal necrosis in liver; other organs appear normal.<br>*Microscopical.*—Anterior-lobe fragment found buried in scar-tissue at the base (serial sections); other organs normal. |
| *Observation 80.*—May 10, 1909. Adult cur; Fig. 8; partial hypophysectomy; the posterior lobe and about two-thirds of anterior lobe removed; no operative complications. | May 11.<br>May 15.<br>May 30.<br>June 21. | 38.6<br>38.6<br>38.2<br>38.6 | 160<br>92<br>82<br>90 | 1000<br>820<br>400<br>240 | 11 lbs.<br><br>12 lbs.<br>12½ lbs. | Promptly recovered from operation; transient polyuria; gain of 1½ lbs. in weight; seemed normal in every particular when sacrificed on June 21. | Sacrificed 42 days following the operation. | Wound healed per primam; about one-third of anterior lobe remains at base; other organs appear normal.<br>*Microscopical.*—Remains of anterior lobe seems normal in every particular; the majority of the cells are small and closely packed with brightly red-staining granules. Other organs normal. |

TABLE VIII.—PARTIAL ANTERIOR WITH TOTAL POSTERIOR LOBE REMOVALS.—Continued.

| Case number and operation. | Date. | Temperature. | Pulse. | Urine. | Weight. | Clinical symptoms. | Duration of life. | Post-mortem conditions. |
|---|---|---|---|---|---|---|---|---|
| *Observation 81.*—May 12, 1909. Adult black and tan; partial hypophysectomy; a fragment of anterior lobe was unintentionally left; no operative complications. (Fig. 38). | May 13.<br>May 15.<br>May 30.<br>June 14. | 38.6° C.<br>38.6<br>38.2<br>38.2 | 182<br>86<br>72<br>86 | 300 cc.<br>260<br>240<br>180 | 14 lbs.<br><br>15 lbs.<br>16 lbs. | No polyuria; no symptoms of cachexia hypophyseopriva; gain of 2 lbs. in weight; a kymographic record of blood pressure and respiration was taken during this operation (cf. Fig. 7); sacrificed on June 14. | Sacrificed 32 days following the operation. | Animal well nourished; no evident remains of the hypophysis; ovaries small, surrounded with fat; other organs appear normal.<br>*Microscopical.*—Dense scar-tissue at base with normally staining anterior-lobe fragments, cells of which appear to be in the active stage of secretion (serial sections). Other organs normal. |
| *Observation 88.*—May 27, 1909. Fox terrier; adult; partial hypophysectomy; dura adherent and friable; venous bleeding at base; apparently the entire gland was removed at operation. | May 28.<br>May 29.<br>May 31.<br>June 2.<br>June 4.<br>June 5.<br>June 8.<br>June 10. | 37.2<br>37.6<br>37.2<br>37.0<br>38.4<br>38.8<br>38.3<br>38.6 | 160<br>180<br>90<br>82<br>100<br>88<br>80<br>96 | 580<br>460<br>650<br>580<br>900<br>820<br>500<br>430 | ..... | Symptoms of cachexia hypophyseopriva appeared immediately after the operation (lethargic subnormal temperature; arching of back; refused food); gradually recovered and from June 4 to 10 was apparently normal. | Sacrificed 12 days following the operation. | Organizing blood-clot at base; no evident remains of the hypophysis. Thyroid large and firm; other organs appear normal.<br>*Microscopical.*—Base, organizing blood-clot with a small area of very much swollen, active-looking anterior-lobe cells; colloid goitre; other organs normal. |
| *Observation 98.*—June 11, 1909. Black and tan bitch; partial hypophysectomy with fragment left; weight 13½ lbs. | June 12.<br>June 22.<br>September 25.<br>December 15.<br>March 15. | 38.2<br>38.2<br>.....<br>.....<br>Sacrificed. | 160<br>116<br>.....<br>.....<br>..... | 1100<br>500<br>600<br>800<br>..... | 13¼ lbs.<br>12¾ lbs.<br>13½ lbs.<br>20½ lbs.<br>24½ lbs. | Transient polyuria and slight loss in weight immediately following operation; not observed during summer; three months later had thick skin, scant hair, dull and stupid, fat; continued to gain in weight; never in heat; definite temperature reaction following subcutaneous injection anterior lobe extract. | Sacrificed after 9 months. | No evident remains of gland; abundant subcutaneous fat; skin thick; thyroid large and colloidal; ovaries small; uterus represented by a shred of tissue. Other organs apparently normal.<br>*Microscopical.*—Minute fragment of anterior lobe in scar-tissue and a few pars intermedia cells (cf. Fig. 42). Pancreas, islands of Langerhans prominent, cells swollen. Thyroid, colloidal. Ovaries, under-developed. Adrenal, medullary cells large and active in appearance. |
| *Observation 100.*—June 15, 1909. Fox terrier; adult; partial hypophysectomy; a fragment of anterior lobe was unintentionally left at the base; no operative complications. | June 16.<br>June 18.<br>June 21. | 38.4<br>38.2<br>38.5 | 142<br>78<br>109 | 1000<br>800<br>640 | ..... | Lethargic; appetite poor; general muscular tremors (rate about 200 to minute); polyuria (640 to 1000 cc.); no sugar in urine; sacrificed June 21. | Sacrificed 6 days following the operation. | Wound healed per primam. A small fragment of anterior lobe remains at base, surrounded with blood-clot; other organs appear normal.<br>*Microscopical.*—The minute remaining fragment of anterior lobe contains normally-staining cells; other organs normal. |


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